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Peri-operative opioid analgesia - when is enough too much? A review of opioid-induced tolerance and hyperalgesia

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Summary

Opioids are a mainstay of acute pain management but can have many adverse effects, including problematic long term use. Opioid tolerance (increased dose needed for analgesia) and opioid-induced hyperalgesia (paradoxical increase in pain with opioid administration) can both contribute to poorly controlled pain and dose-escalation. Hyperalgesia is particularly problematic as further opioid prescribing is largely futile. The mechanisms of opioid tolerance and hyperalgesia are complex, involving mu opioid receptor signalling pathways that offer opportunities for novel analgesic alternatives. The intracellular scaffold protein, beta-arrestin 2, is implicated in tolerance, hyperalgesia and other opioid side effects. Recent development of agonists biased against recruitment of beta-arrestin 2 could provide analgesic efficacy with fewer side effects. Alternative approaches include inhibition of peripheral mu opioid receptors and blockade of downstream signalling mechanisms, such as the non-receptor tyrosine kinase, Src, or N-methyl-D-aspartate receptors. In light of their detrimental effects, it is prudent to use multimodal analgesic regimens to reduce reliance on opioids during the perioperative period. This review focusses on clinical and mechanism-based understanding of tolerance and OIH, and discusses current and future strategies for pain management. **Word count: 181**

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The evolution of opioid analgesia

Humans have used opioid alkaloids in resin harvested from the poppy, Papaver somniferum, for thousands of years to suppress pain and for their hedonic effects. Merck began extracting morphine in the 1930's and the first synthetic opioid analgesics appeared soon after. Despite having disparate structures, all these opioids bind to mu opioid receptors. Mu receptors are class A (rhodopsin family) G protein coupled receptors (GPCRs). They are essential for the analgesic actions of opioids, being expressed at key locations within the pain pathway (1). Their activation suppresses both the reflexive and affective components of pain. However, the respiratory centres in the brain stem, the gut and the chemotrigger zone, also contain mu receptors, activation of which gives rise to respiratory depression, constipation and nausea (2) . Opioid analgesics have additional detrimental effects including tolerance (increasing doses are required to maintain analgesia), dependence (physical and/ or psychological), hyperalgesia (a paradoxical increased sensitivity to pain) (figure 1) and addiction (inability to control continued use, despite harm or negative consequences) (1, 3). Repeated or prolonged administration of opioids increases the likelihood of these detrimental effects and leads to withdrawal when treatment stops. At the cellular level, the adaptive changes participating in opioid tolerance lead to dependence and withdrawal upon cessation of opioid exposure (4). By contrast, at the systems level, there are distinct processes required for the acquisition of analgesic tolerance and dependence (as evidence by antagonist precipitated withdrawal), despite overlap in the mechanisms required for their expression (5).

Given the adverse effects associated with opioid use it is logical to look for alternative approaches to treat severe pain. While there are other targets within the pain pathway for the future development of drugs, including the delta and kappa opioid receptors (6), mu agonists are a tough act to follow. Despite considerable investment, no new drugs have usurped them as the preeminent analgesics for treating severe pain, particularly in the acute setting. This is perhaps not surprising considering the strategic location of mu receptors and the role of the endogenous opioid system in regulating pain sensitivity (1).

Opioid analgesia in the 21st century

Chronic pain, including persistent post-surgical pain (as reviewed in Glare et al Lancet 1(7)), affects at least 20% and perhaps up to 50% of the population, (8). It is a major public health problem, being the leading cause of global disability (9). As a long term condition it needs to be properly managed to maximise function and quality of life. A focus on supported self-management and increase in activity levels may be a more useful approach for patients and healthcare professionals. Despite this, many patients with chronic pain are prescribed an opioid. Opioids are now one of the most commonly prescribed medications in the US, with similar, although less marked, trends in other countries including the UK (10) (11). While pain reduction by pharmacological means may be advantageous, there is limited evidence for long term benefit of opioids, with evidence of harm, particularly at higher doses (12).

There have been unintended consequences of a liberal prescribing policy, particularly in the US, where long term harms from prescription opioids have become much more apparent, including addiction, misuse and increased mortality (13). (14)." While opioid use in chronic pain may appear to be distinct from the perioperative setting, prolonged opioid exposure creates additional challenges when trying to manage acute pain (15, 16) (17). Furthermore, we need to consider what role surgery and postoperative opioid prescribing play in initiating long term opioid use (table 2)(18), as covered in detail elsewhere in this series(19).

The use of synthetic (e.g. fentanyl, remifentanil) or natural (e.g. morphine) opioids during the perioperative period provides a component of balanced anaesthesia and analgesia. Timely opioid administration during surgery reduces the dose of general anaesthetic needed, enabling faster recovery (20), while ~~on-demand~~ patient-controlled postoperative opioid analgesia improves comfort and patient satisfaction (21). However, the use of perioperative opioids may predispose to long term opioid use. In the USA, opioid prescribing for minor surgery, has increased: up to 75% of patients are

prescribed opioids at hospital discharge, with the risk of misuse increasing by 44% for each week and repeat prescription after discharge (16, 22). Cooperation between surgeons and anaesthetists working with primary care physicians is needed to reduce postoperative opioid use, and ensure early identification and management of adverse effects or problematic use(15) (23). However, linkage of perioperative anaesthesia and analgesia to long term outcomes such as opioid prescribing, using routinely collected heath care data, is currently limited.

This review will focus on the use of opioids in the perioperative setting, particularly on clinical and mechanism-based understanding of tolerance and OIH. By improving understanding of the underlying mechanisms, it may be possible to develop strategies to identify and better manage postoperative and post-injury pain in order to improve efficacy and safety of opioid use, and to minimise long term harms.

The opioid signalling system

Before exploring mechanisms of tolerance and OIH, it is important to consider the intricacies of opioid signalling. Components of the system can be found in ancient species, including jawless fish, evidence that this endogenous pain control mechanism has evolved over hundreds of millions of years (24). Three genes encode endogenous opioid peptides (25), most of which have some activity at each of the three main opioid receptor subtypes (mu, kappa and delta) with some subtype preferences.

Opioid analgesics activate mu receptors leading to inhibition of adenylyl cyclase and high threshold voltage activated Ca^{2+} channels (VACCs) and activation of inwardly rectifying K^{+} channels (1). Inhibition occurs through G-proteins, which upon activation dissociate into component $G\alpha_{i/o}$ and $\beta\gamma$ subunits (figure 2).(26). The result is decreased neuronal excitability, with reduced excitatory neurotransmitter release in pain pathways (27, 28). By contrast, activation of mu receptors in the brain's reward circuitry, , inhibits inhibitory neurotransmission in the ventral tegmental area, reducing the frequency of GABAergic inhibitory postsynaptic events, thereby disinhibiting

dopaminergic neurones and increasing dopamine release into the striatum and prefrontal cortex (table 1) (29, 30). Enhanced dopamine release causes D2 receptor-dependent reinforcement (31). However, morphine also has reinforcing effects in mice engineered to lack dopamine, an observation that implicates alternative mechanisms(32).

Consequences of prolonged opioid exposure

The mu receptor has several serine, tyrosine and threonine sites of phosphorylation, mostly in its C-terminus, which interfaces with the G protein (1, 26).

Opioid receptor activation can lead to phosphorylation by GPCR kinases (GRKs), MAPK, JNK, PKA, PKC, Src and Ca^{2+}/calmodulin dependent kinase II (CAMKII) (Zhang et al., 2017). Furthermore, inhibition of several of these kinases reduces tolerance and/or hyperalgesia (see Panel) (1, 33-36). Mu receptor phosphorylation by GRKs, of which there are seven forms, leads to β-arrestin2 recruitment, receptor endocytosis and additional kinase-driven signalling events (figure 2). After endocytosis receptors are either degraded or recycled back to the cell membrane. Decreased mu receptor expression at the cell membrane may contribute to tolerance. Indeed, mice lacking 50% of their mu receptors exhibit more rapid and profound morphine tolerance than wild type mice (30). In humans, the endogenous opioid system contributes to pain sensitivity (37) and a loss of mu receptors, caused by prolonged exposure to opioid analgesics, might also heighten sensitivity to pain leading to OIH. Indeed, tolerance caused by endogenous opioids has been implicated in the hypersensitivity of patients with fibromyalgia (38). However, morphine, which causes tolerance and OIH, has little effect on mu receptor endocytosis even with prolonged exposure (39). By contrast, the selective peptide agonist DAMGO, produces marked receptor endocytosis with little tolerance and therefore the relationship between endocytosis and tolerance is complex. Endocytosis may in fact be required to reverse desensitisation, a rapid form of tolerance observed at the cellular level (40).

Opioid Tolerance

Tolerance to the effects of opioids occurs, with an increased dose required for the same amount of analgesia (figure 1), but this can vary dependent on both pharmacokinetic and pharmacodynamic factors (41). Furthermore, the extents and rates of the development of tolerance differ for different opioid effects. Differences in tolerance to respiratory depression and analgesia may be explained by their differing molecular mechanisms (42). Tolerance to the analgesic effect is problematic, whereas tolerance to unwanted side effects, such as respiratory depression and sedation, can be useful to enable dose increases when required, to improve analgesia. This may be unpredictable, with a narrow therapeutic window between desired effects (usually analgesia) and undesirable respiratory or gastrointestinal effects (43). Acute tolerance may be hard to distinguish from other opioid related effects, such as OIH (table 3). Key features to assess include the response to additional opioid: with tolerance, an increased opioid dose should be effective, although very high doses may be required (figure 1); similarly, a reduction in opioid dose would be expected to produce increased pain (but not hyperalgesia). Additionally, in patients with tolerance, but lacking OIH, apart from around the immediate injury site, there should be no signs of reduced pain thresholds/hyperalgesia (44).

How does chronic opioid use affect pain sensitivity

Patients presenting for surgery, who are on long term opioids, are likely to have aberrant somatosensory responses to painful stimuli. In a large population-based study, opioid use was associated with increased pain sensitivity compared to patients taking non-opioid analgesics. This may reflect OIH (figure 1), or a pre-existing reduction in endogenous pain inhibition, increasing the likelihood of long term opioid use (45). Non-opioid perioperative analgesia may be most beneficial in these patients.

In patients receiving long term opioids, dose-reduction or cessation can reduce pain sensitivity, with many patients reporting improvements in pain, and few experiencing worsening of their pain (46, 47). A recent clinical trial of opioid use for chronic musculoskeletal pain found that patients on long

term opioids had no improvement in function, worse pain, and more adverse events than those receiving non-opioid analgesics (48). The risk of developing chronic post-surgical pain, in addition to OIH and tolerance, must also be considered, with a role for transitional pain clinics to ensure correct opioid management (see Glare et al (7))

Interestingly, in some chronic pain states there is evidence that dysfunction in the endogenous opioid systems may lead to development of hyperalgesia, with a potential site for this within the brainstem (38, 49). The implications for acute management of patients on chronic opioid therapy is that, regardless of whether increases in pain sensitivity are due to a pre-existing vulnerability, or a consequence of opioid therapy, care must be taken in managing these patients to avoid further opioid-related complications such as OIH.

Identifying Hyperalgesia in Patients

While there is extensive preclinical evidence of OIH, with changes in the underlying neurobiology leading to a pro-nociceptive state (table 1), as well as human volunteer studies, there is still debate about the clinical manifestations of OIH. This may be at least partly due to some studies failing to make an adequate distinction between increased pain severity and hyperalgesia. Many studies have used only pain scores and postoperative opioid consumption as surrogate markers of OIH, which do not take into account other potential causes such as inadequate analgesia, changing underlying disease pathology, or acute tolerance. To make a clinical diagnosis of OIH, a distinction needs to be made between high pain scores, and altered sensory processing with allodynia and/ or hyperalgesia (50). There may be some merit in the use of techniques such as quantitative sensory testing (QST), to assess patient responses to defined physical stimuli (thermal, mechanical), aiming to move towards a more consistent approach to diagnosing OIH (44). Even with QST, the demonstration of hyperalgesia around the surgical site is not necessarily diagnostic of OIH, as the tissue response to surgical trauma, with release of inflammatory mediators can cause peripheral and central sensitization may be manifested as hyperalgesia. If there is more widespread hyperalgesia, then

there is an increased likelihood of OIH (51). Another potential differentiating feature is if pain worsens with further opioid dosing, rather than displaying the expected dose–response relationship for analgesia (figure 1). Clinical criteria for diagnosing OIH using these features have been suggested (52). The lack of a specific test adds to diagnostic uncertainty, coupled with some overlap in symptoms between OIH, tolerance, acute opioid withdrawal and acute neuropathic pain, all of which may occur in the perioperative setting (table 3). This uncertainty is compounded by the observation that neuropathic pain often responds poorly to opioids(53).

Clinical evidence for OIH

Identification and management of OIH is important, as untreated, it may increase the risk of developing persistent post-surgical pain (7) . As outlined in table 3, care is needed to ensure that OIH is recognised and appropriately treated. There is however continued debate as to whether OIH is a significant clinical entity (54).

Outside the acute surgical setting, a systematic review identified 8 studies with evidence of OIH, but the approach to diagnosis was inconsistent and with limited assessment of impact (55). Small studies using QST in a range of chronic pain conditions indicate that opioid use does contribute to hyperalgesia, although this may be enhanced by other factors such as low mood. Sex differences may also occur, with opioid prescribed males showing increased hyperalgesia with fentanyl compared to females, and both showing reduced pressure pain thresholds, compared to healthy controls (56-58). Increased thermal sensitivity has also been shown in patients on long term opioids, even after adjusting for a variety of other factors (59). This action may be a consequence of recruitment and sequestration of beta-arrestin 2 following mu receptor activation, which has been shown in mice to sensitise TRPV1 channels to thermal activation (60).

A more recent comprehensive systematic review of OIH after surgery identified 27 studies with ~1500 patients. Higher doses of intraoperative opioid were associated with an increase in postoperative pain scores, and higher 24 hour morphine consumption. This association was seen

mainly with remifentanil (61). There were similar findings in a subsequent systematic review of acute OIH and tolerance (62). A large study using the PAIN OUT database (see http://pain-out.med.uni-jena.de/) found an association between worse pain-related outcomes and intraoperative use of remifentanil (63). More recent studies have strengthened this finding, with younger patients seeming to be at higher risk (64). The cause of the apparent higher risk of OIH with remifentanil compared to other opioids is unclear, but may be related to the fast onset/ offset of its action.

Can we prevent OIH?

Following the premise that prevention is better than cure, strategies to minimise perioperative opioids and utilise alternative analgesia should be considered, aiming for opioid-free or low dosing regimens, as outlined in see table 4 and figure 3) (65). Anaesthetic technique should be considered: intravenous anaesthesia with propofol may have a lower risk of OIH when compared to anaesthesia with a volatile agent. Addition of (51, 66) nitrous oxide may reduce the incidence of hyperalgesia (67, 68). (69)

If intravenous opioid infusion is being considered as part of the anaesthetic regimen, then avoiding higher infusion rates of remifentanil may reduce risk of OIH. Dose rates of more than 0.2 μg/kg/min may increase risk of OIH, and for doses of more than 0.25 μg/kg/min, acute tolerance may be problematic (70). Consideration of a gradual tapering of remifentanil at the end of surgery may also reduce OIH, possibly by reducing withdrawal induced long term potentiation at the first central synapse in the spinal cord(71, 72) (73). Other suggested strategies to reduce this problem include limiting the dose of remifentanil, or specifically targeting putative mechanisms using novel approaches (74).

Current options for treating tolerance and OIH

Acute tolerance makes postoperative pain control challenging. Poor pain control and high opioid requirements after surgery are associated with persistent postsurgical pain (7). If OIH is suspected in

the immediate postoperative period it is important to address this as soon as possible. Untreated OIH makes perioperative management more difficult, with potential delay in hospital discharge.

Early assessment and diagnosis is important in order to effectively direct treatment. While there is significant overlap in the approach to tolerance and OIH, one of the key differences is that OIH may require opioid dose reduction. A reasonable first step therefore is to assess the response to an increased opioid dose: if analgesia improves, then tolerance is more likely; if analgesia worsens, then OIH should be suspected, and other features sought.

Use of multimodal analgesia with low or no opioid component: Current strategies have not been extensively explored with clinical studies, regarding the impact on OIH and tolerance, but include the use of many of the agents outlined in table 4. These include simple analgesics such as paracetamol and NSAIDs, dexmedetomidine, NMDA receptor antagonists (e.g. ketamine), and opioid dose reduction (74-77). Opioid free multimodal analgesia may be a laudable aim, but the number of patients presenting for surgery who are not opioid naïve will pose a challenge. A small RCT has shown it is possible to significantly reduce opioid consumption in such patients by using intravenous ketamine (78). Furthermore a Cochrane review found that ketamine may reduce the risk of persistent post-surgical pain, although the majority of studies were small, with possible overestimation of treatment effect (79). Use of more than one type of non-opioid analgesic may have most impact on opioid consumption, although there are a limited number of studies assessing combination analgesia. Use of at least two non-opioid approaches may reduce adverse effects, such as respiratory depression, gastrointestinal dysfunction, as well as reducing opioid requirements (80, 81).

Consideration of non-pharmacological strategies: whilst not the focus of this review, there is some evidence that use of psychosocial techniques, such as relaxation, behavioural instruction and patient education can be beneficial in reducing post-operative pain(82, 83). The development of Enhanced Recovery After Surgery (ERAS) protocols using a multimodal approach to minimize impact of the

surgical episode does incorporate optimising analgesia, but also uses early mobilization and other techniques which may indirectly improve pain outcomes (84).

Future approaches to managing OIH and tolerance

There are several overlapping pathways implicated in the opioid induced tolerance and hyperalgesia (Panel), many of which have recently been extensively reviewed (1, 33-35). These pathways have been implicated in enhanced pronociceptive systems (e.g. TRPV1, NMDA receptors and microglia) and diminish antinociceptive systems (e.g. beta-arrestin 2). Any of these pathways may provide targets for adjunct agents that improve opioid analgesia or their recruitment may be avoidable by agonists biased against their activation. We will focus here on recently emerging targets affecting the endogenous opioid system, which may offer opportunities for developing new approaches to improved analgesia.

Arrestins, opioid side effects, tolerance and OIH

There are four arrestins, two acting on rhodopsin within the visual system and two preferentially interacting with other GPCRs including beta-adrenergic and opioid receptors, (arrestins 2 and 3); commonly referred to as beta-arrestin1 and 2 (85). Receptor phosphorylation via GRK enables recruitment of beta-arrestin2, an event that precedes endocytosis and blocks G protein interactions (figure 2) (1). Mice lacking beta-arrestin 2 exhibit hypoalgesia and a striking resistance to morphine tolerance, respiratory depression and constipation (30, 86-88). Intrathecal beta-arrestin 2 reduction also attenuates morphine tolerance in rats, indicating that this effect is not a consequence of compensatory mechanisms in arrestin-deficient mice (89). This approach also reduced withdrawal symptoms in rats chronically administered morphine. This suggests that morphine analgesic tolerance and dependence involves beta-arrestin 2. In addition, beta-arrestin 2 also facilitates the development of pain sensitivity in mice by facilitating TRPV1 activation (60).

Biased agonism

There is increasing evidence that some "biased" GPCR agonists preferentially activate either G protein-mediated signalling or recruitment of beta-arrestins (67, 68). (87, 90).

The demonstration in rodents of a role for beta-arrestin 2 in the side effects and other complications of opioids led to a search for biased mu receptor agonists. The first, herkinorin, activates G proteins with negligible recruitment of β-arrestin 2. It is analgesic with markedly decreased tolerance compared to morphine (91). Herkinorin also exhibits less constipation and respiratory depression (92). Two more biased agonists, TRV130 and PZM21 (93) also appear to cause less respiratory depression and constipation than morphine; however, respiratory effects and tolerance were observed for PZM21 in a recent study (Hill et al., BJP 2018). TRV130 causes less tolerance than morphine when administered repeatedly to rodents and was analgesic when administered intravenously to treat acute pain, in a phase 2 clinical studies (91). However, there have been no studies in chronic pain, which would be helpful for identifying beneficial properties relating to tolerance and OIH.

Targeted modulation of signals that trigger hyperalgesia and tolerance

An alternative to developing agonists biased against beta-arrestin 2 is to inhibit signalling components to minimise the side effects, tolerance and OIH of available opioids (figure 2). However, beta-arrestin 2 provides a scaffolding role and is not a signalling molecule in its own right and is unlikely to be a fruitful pharmacological target. Instead, molecules upstream or downstream of beta-arrestin 2 recruitment may prove more suitable targets.

The use of naloxone, to antagonise the mu receptor, provides prolonged oxycodone analgesia and reduces constipation, effects that appear to be mediated through inhibition of peripheral mu receptors (94) (95). There may be value in exploring the use of naloxone or methylnaltrexone, a peripherally restricted mu receptor antagonist, in combination with opioid agonists to reduce tolerance and hyperalgesia (figure 1). Methylnaltrexone inhibits morphine tolerance and OIH in mice

by antagonising mu receptors specifically on TRPV1 expressing primary afferent nociceptive neurones (95). It remains to be seen whether naloxone or methylnaltrexone will be effective in clinical studies of morphine tolerance and hyperalgesia.

Although most evidence suggests not, antagonism of peripheral mu receptors may compromise opioid analgesia (95). An alternative is to inhibit downstream targets such as c-Src, a member of the Src family of non-receptor tyrosine kinases (SFKs). SFKs participate in cell proliferation and differentiation and are widely expressed throughout the nervous system, where they regulate sensory function (96). SFKs can be activated by GPCRs, via Gα and Gβγ subunits (97) and are involved in activation of intracellular signalling processes through formation of complexes with β-arrestin 2 (figure 1). Src participates in opioid receptor phosphorylation, endocytosis, tolerance, and withdrawal (36) (30, 98, 99).

Dasatinib, a Src inhibitor used clinically to treat leukaemia (100), not only attenuates tolerance in mice, but, when administered before morphine, also rapidly restores analgesia diminished during the preceding days (30). Unlike deletion of β-arrestin2, which enhances morphine reinforcement in mice, Src inhibitors appear to have no such effect. However, similar to the reduced expression of beta-arrestin 2, Src inhibition diminishes opioid withdrawal in rats (36) (Zhang et al., 2017). Additional work is needed to establish whether Src participates in other opioid side effects such as constipation and respiratory depression. Src has also recently been implicated in the role of microglia in morphine analgesic tolerance (see Panel)(101).

While Src inhibitors are not anti-nociceptive in acute pain (30), they reduce hyperalgesia in rodent models of OIH, neuropathic, inflammatory and bone cancer pain (102-104). Hyperalgesia is associated with Src-mediated phosphorylation and up-regulation of NMDA receptors, which leads to enhanced excitatory transmission in spinal neurones (105). Several parallels can be drawn between hyperalgesia and morphine tolerance (see Panel), including a common requirement for Src and NMDA receptor activity (106) (figure 2). The ability of Src inhibitors to reduce hyperalgesia and

reverse tolerance, thereby restoring analgesia, makes them promising candidates as adjuncts to opioid analgesics. Future clinical studies will be required to establish whether Src inhibitors mitigate the detrimental effects of prolonged opioid exposure.

Inhibitors of the mammalian target of rapamycin (mTOR) are additional examples of anticancer medications that show preclinical promise as adjuncts to reduce tolerance and OIH (figure 2)(107). mTOR, which governs most protein translation, becomes activated in rat spinal dorsal horn neurones after repeated intrathecal morphine injections. Its inhibition reduces morphine tolerance and the associated OIH.

Where are we now?

While opioids are good analgesics, there are risks associated with their use. In the acute setting the challenges include:

1. Postoperative pain management of patients who are on chronic opioids. Issues to be addressed include opioid tolerance, increased risk of acute withdrawal, and OIH.
2. Minimising the risk of the acute surgical episode leading to prolonged opioid use, due to tolerance, OIH and/ or prolonged prescribing for other reasons.

The approach to both of these may be similar, aiming for optimal perioperative analgesia, using techniques and agents to minimise opioid use (see figure 3). The optimum combination is likely to vary depending on the type of surgery, and a range of patient factors (co-morbidities, pre-existing pain/ analgesics; genetics, psychosocial issues). It is also important to ensure that there are systems in place after discharge, so that any increase in opioid use for acute pain management has a clear tapering plan. Modification of discharge analgesic prescribing should be considered with the minimum effective dose of opioid, for the shortest possible duration. Patient education around the risks of prolonged opioid use would be prudent. Early identification of any problematic or prolonged use, with access to appropriate support in opioid reduction when needed, should always be considered.

Agenda for the future

It is clear that there are a number of research gaps that must be addressed in order to improve the current situation. This may improve not only peri-operative patient management, but also contribute to addressing the wider societal problems with chronic opioid use. We have highlighted a number of specific research gaps that relate to the focus of this review:

1. Develop novel analgesic targets: Improved mechanistic understanding of OIH/ tolerance to direct development of novel analgesics using the endogenous opioid systems. There is some progress in this area in the preclinical field, as outlined earlier in this review, but translation to the clinical setting is required.
2. Understanding the impact of peri-operative analgesia (and anaesthesia) on long term health (and social care) outcomes, such as persistent opioid use (and persistent pain): Analysis of large population based data may be required. Options include the use of routinely collected health and social care data (at national and potentially international level), to link acute hospital and community based care episodes and advance our understanding of the impact of perioperative management on long term health outcomes. Approaches to ensure that these data are robust and accurate need to be considered. Other alternatives include developing research resources by national and international collaboration (such as the UK Biobank project). Both of these approaches are likely to require collaboration between policy makers, clinicians and academics.
3. Understanding (and modifying) risk factors to opioid use at an individual level: Use of a precision medicine approach to identify high risk individuals and evaluate targeted, individualised strategies. This may involve testing the use of complex interventions, rather than a single approach.

Nevertheless, for managing pain in the acute setting, opioids are often the best currently available analgesics. This is perhaps not surprising, given the key role that endogenous opioids play in pain

processing at all levels. Better understanding of the impact of opioids, at neurobiological, clinical and societal levels is required to improve future patient care.

Table 1: **Opioid effects with acute and chronic exposure.** Some key processes contributing to analgesia and the detrimental effects of opioids (1, 33).

Opioid paradigm	**Behavioural effect**	**Possible mechanisms**
Acute administration	Analgesia	↓Excitatory transmission in pain pathway
	Nausea	Chemoreceptor trigger zones
	Respiratory depression	Brain stem nuclei
	Constipation	Inhibition of myenteric neurons with ↓ACh
	Reward	↓Inhibitory transmission in VTA and ↑DA
	Rapid tolerance & OIH	See Panel
Chronic administration	Tolerance, dependence & OIH	See Panel
	Constipation	Inhibition of myenteric neurons with ↓ACh
End of treatment	Withdrawal	↑Glutamate, ↑NA, ↑CRF, ↓DA, ↓5-HT

OIH, opioid-induced hyperalgesia, ACh, acetylcholine, VTA, ventral tegmental area, DA dopamine, GRK, G protein receptor kinase, β-arr2, beta-arrestin 2, cAMP, cyclic adenosine monophosphate, CREB, cAMP response element binding protein, NMDAR, N-methyl-D-aspartate receptor, NA, nor adrenaline, CRF, corticotrophin-releasing factor, 5-HT, 5-hydroxytryptamine

Table 2: Opioid use in the acute setting

Clinical issues	Factors to consider

Acute presentation of patient on regular opioid prescription: i.e. not opioid naïve	• Pain control difficult
	• Likely to have pre-existing tolerance:
	  ○ higher doses needed to achieve analgesia
	• may have OIH:
	  ○ need for reduced opioid dose/ alternative strategies

Opioid naïve patient treated with short acting perioperative opioid as part of the anaesthetic regimen	• Acute tolerance • Development of OIH • If rapid cessation: Acute opioid withdrawal
Opioids prescribed to allow early discharge	• Increased prescribing of opioids for longer post-operative period leading to sustained use • Dependence (physical and/ or psychological) • Increased potential for drug diversion if opioids not used by patient for whom prescribed

Table 3: Differential diagnosis of inadequate post-operative pain control. COWS = clinical opioid withdrawal scale(108)

Clinical Syndrome	Clinical features	Suggested management approach	References
OIH	• Hyperalgesia in response to opioid administration, or increased opioid dose; • may not be at site of pre-existing pain/ injury; • descriptors used may be neuropathic in nature	Reduce opioid dose; Use adjuvants targeting mechanisms (eg reduce NMDA receptor activity via agents such as ketamine); Mixed evidence for opioid rotation (mainly long term use)	(54, 109, 110)
Tolerance	• Increased opioid dose required to achieve the same level of analgesia; • Despite no change in underlying cause of pain; • Can occur in both acute and chronic settings	Increase opioid dose; Rotate opioid; Use adjuvants targeting mechanisms	(41)
Acute Neuropathic pain	• Signs and symptoms compatible with neuropathic pain; • Known injury/ damage to the peripheral or central nervous system; • Defined area affected	Consider use of screening tools for non-specialists; Use specific anti-neuropathic medication e.g. gabapentinoids, ketamine (although evidence is inconclusive for acute pain)	(77, 79, 111)
Acute Opioid Withdrawal	• An increase in local and/ or widespread pain; • Often associated with anxiety and distress, gastro-intestinal upset; autonomic dysfunction	Assess using COWS scale; Reduce rate or size of opioid reduction; Symptomatic relief of withdrawal symptoms	(46, 108, 112)

Table 4: Some suggested analgesic approaches for multimodal analgesia to reduce opioid use.

Agents/ technique	**Postulated mechanisms of analgesia**	**Comments; references**
Simple analgesics		
Paracetamol	Possibly central inhibition of COX-mediated prostaglandin production	High quality evidence for analgesic benefit of intravenous paracetamol and limited opioid sparing effects (21, 113)
NSAIDs	Inhibition of COX enzymes to reduce inflammatory cytokines/ chemokines	Potential issues with renal dysfunction, GI irritation(114)
Anti-neuropathic agents and nonstandard analgesics		
Gabapentin; pregabalin	Inhibition of presynaptic Ca^{2+}	Unclear as to optimum dose and timing/ duration(115)
Ketamine, Magnesium	NMDAR inhibition	Unlikely to be sufficient in isolation; (77, 116)
Dexmedetomidine, clonidine	α2 adrenergic agonist	Sedative; postural hypotension (65)
Steroids	Reduce inflammatory response to surgery	Consider impact on immune function; (117)
Intravenous lidocaine	Na^+ channel blockade	(118) Low to moderate quality evidence of reduced pain, but variable reports of effects on opioid use.
Invasive techniques		
Nerve Blocks with local anaesthetic	Blockade of action potentials: Na^+ channel blockade	Extent depends on type of LA used, dose, volume, route etc Single shot or catheter/ infusion based techniques/ PCEA. (119)

NMDAR, N-methyl-D-aspartate receptor, COX, cyclooxygenase, LA, local anaesthetic, PCEA, patient-controlled epidural analgesia.

Panel: Cellular mechanisms implicated in tolerance and hyperalgesia

Mu opioid signalling

- ↑cAMP / PKA
- PKC
- JNK
- β-arr2*
- Src*

Transcriptional mechanisms

- CREB
- mTORC1

Pronociceptive ion channels

- NMDA receptors
- TRPV1

Microglia

- TLR4
- P2X4 / P2X7
- Src
- BDNF

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