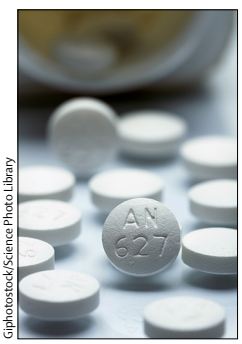
Best practice in managing postoperative pain



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Controlling acute pain after surgery is important not only in the immediate postoperative phase but also to prevent chronic postsurgical pain, which can develop in as many as 10% of patients. A Series of three papers in this week's issue examines postoperative pain management, outlines how and why acute pain can become chronic, what can be done to lessen that risk, and the role of opioids.

In many countries, opioid misuse is escalating, causing thousands of deaths annually. As the Series explores, excessive prescribing of opioids for pain control after surgery is now recognised as an important driver of opioid misuse and related harm. For many, "opioid dependency started with a prescription after minor trauma or surgery", as Markus Hollmann and colleagues outline in a Comment. Dependency often results in patients requesting repeat prescriptions or buying more opioids online or on the street. Despite attempts to prevent the illegal sale of opioids, online sales are rising in the USA—for example, with the availability of tramadol being a particular problem.

Improvements in perioperative prescribing and a reduction in opioids on and after discharge are needed to have a tangible effect on the opioid epidemic. Some US states, for example, impose limits on how many pills physicians can prescribe per day, and others make continuing medical education a requirement for physicians prescribing controlled substances. The Centers for Medicare and Medicaid Services require consultation between pharmacists and prescribers about high morphine doses in daily prescriptions for many chronic pain patients.

Pain is a highly personal and subjective experience, which is increasingly recognised to be shaped by life events, mood, fear, anxiety, and anticipation, among other influences. Management of postoperative pain is best tailored to the individual, with multimodal non-opioid analgesics used first. Local anaesthesia might have a role, followed by careful prescription of tapering doses of opioids, if needed. Moreover, communication between hospital and primary care needs to improve to ensure opioid prescribing is carefully managed in the community. ■ *The Lancet*

Artificial intelligence in global health: a brave new world

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Despite decades of progress in global health, many low and middle income countries are not reaching their health Sustainable Development Goals, creating a sense of urgency to prioritise health in resource-strained environments. The use of artificial intelligence (AI) is becoming increasingly attractive to the health-care industry. The accompanying enthusiasm remains awkwardly placed somewhere between aspiration and reality.

The Artificial Intelligence in Global Health report, published on April 1, 2019, was funded by the USAID's Center for Innovation and Impact and the Rockefeller Foundation, in close coordination with the Bill & Melinda Gates Foundation. The report looks at 27 cases of AI use in health care and distils them into four key groupings—population health, patient and front-line health worker virtual assistants, and physician clinical decision support. It hypothesises how AI solutions could improve access, quality, and efficacy of global health systems while accounting for their technological maturity and feasibility. The identified challenges, the most highly volatile being privacy, ethics, and data ownership, are in line with recent debates on regulation and policy for AI technology implementation in health care. To mitigate these challenges, stakeholders would need to be held accountable and be transparent whether supporting innovation, interoperability, or capacity building. The report sets the framework for a proactive and strategic approach to accelerate the development of cost-effective use of AI in global health by investing in case-specific, systematic, and technology-related key areas.

This report outlines an aspirational yet pragmatic framework for better coordination for AI investment between donors, governments, and the private sector, while harnessing a futuristic vision—the digitisation of global health. Because the cost-effectiveness of these AI solutions has yet to be validated, the call for investments feels somewhat premature. Traditionally, the global health community is a late adopter of new technologies. Hence, it is imperative that they have an integral and active role in the dialogue early on. As this report rightfully stipulates, technology will get there, but will the world follow? ■ *The Lancet*

For the **report** see https://www.usaid.gov/sites/default/files/documents/1864/AI-in-Global-Health_webFinal_508.pdf

For more on **AI regulation and framework debate** see **Online/Comment** *Lancet* 2019; published online March 29. http://dx.doi.org/10.1016/S0140-6736(19)30762-7

linked, population-level databases, is required. The investigators acknowledge these limitations in their report.

The results of this study, in conjunction with results of studies of pregnancy interval after early loss and with findings of studies using new approaches to study interval after a livebirth, suggest that interpregnancy interval might be less important than previously assumed, at least for women in high-income regions. Rather than adhering to hard and fast rules, clinical recommendations should consider a woman's current health status, her current age in conjunction with her desires regarding child spacing and ultimate family size, and particularly following a loss, her emotional readiness to become pregnant again.

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I have prepared a grant application to the US National Institutes of Health, currently pending, to study the association of interpregnancy interval with pregnancy outcome. I declare no other competing interests.

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Optimal postoperative pain management: redefining the role for opioids

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Fear of pain is deeply rooted among patients who are about to have surgery.[1] Satisfactory perioperative pain management is crucial to assuring a good patient experience, optimising postoperative outcomes, and enhancing functional recovery after surgery.[2] Despite decades of research showing the benefits of various new analgesic strategies, many patients endure severe postoperative pain,[3] and this holds true across all age groups and continents, even after surgery widely considered to be minor.[4] A 2016 study from the USA, which enrolled 799 449 patients, showed that reliance on opioid analgesics as the mainstay for perioperative pain management is still widespread.[5] This situation is worrying because several countries, most prominently the USA, Canada, and Australia, are struggling with an opioid crisis of unprecedented proportions.[6] There are an estimated 2 million patients in the USA who have an opioid use disorder,[7] with approximately 90 deaths occurring every day in the USA from an opioid overdose.[8] For many of these individuals, opioid dependency started with a prescription after minor trauma or surgery, highlighting the pivotal role of the health-care system in this epidemic.

In *The Lancet*, a new Series on postoperative pain management and opioids[3,6,9] details the current state of perioperative pain management with a strong focus on opioids, their role as analgesics, and the problems that accompany their widespread use. Paul Glare and colleagues[3] revisit the rationale for the use of opioids and other analgesics: to alleviate acute postsurgical pain and disrupt the transition from acute to chronic postsurgical pain. As the authors explain, it is now firmly established that poorly controlled acute pain after surgery is among the strongest predictors for the development of chronic postsurgical pain, but simply using escalating doses of opioids might only

worsen the problem. Mark Neuman and colleagues[6] recount how opioid overprescribing after surgery emerged and delineate prescribing, hospital, and public policy interventions to standardise and decrease the dispensing of opioids after surgery. Both groups of authors[3,6] advocate for an approach that includes transitional pain clinics for patients at high risk for prolonged opioid use after surgery as a model for the future.[10] Lesley Colvin and colleagues[9] review the basic mechanisms that underlie the adverse effects of opioid use, including opioid-induced hyperalgesia and tolerance. As our understanding of the limitations of opioid use has grown, multimodal analgesic regimens are increasingly used, helpful in decreasing opioid dose[11] and could be the key to avoiding long-term dependence.[10] By combining non-opioid analgesics with targeted regional anaesthetic techniques, multimodal analgesic regimens target multiple sites along the nociceptive pathway with the net effect of limiting opioid dose, improving analgesia, and enhancing safety.[11] Better understanding of the basic mechanisms underlying opioid-induced hyperalgesia and tolerance, including the role of the β-arrestin pathway, has led to the development of biased agonists that could provide similar analgesic effects to opioids with fewer side-effects in the future.[9]

Currently, the best approach is multimodal analgesia. The first component of an effective multimodal analgesic regimen should be one or two simple non-opioid analgesics: in the absence of contraindications, acetaminophen, a non-steroidal anti-inflammatory drug, or a cyclo-oxygenase-2 inhibitor. An adjuvant analgesic, such as an antiepileptic, α2 agonist, or ketamine, is often added, on the basis of the procedure and patient's risk profile. Advanced techniques such as neuraxial (spinal and epidural) anaesthesia and analgesia, nerve blocks, and wound infiltration should be integrated into the multimodal analgesic regimen whenever feasible. Wound infiltration with local anaesthetic and regional analgesia can provide excellent dynamic pain relief, but care must be taken to align the duration of these advanced analgesic methods with the anticipated time course of pain, and the techniques must be meaningfully integrated into the overall plan of care.[12] Opioids should be used as rescue medication, intravenously for as short a time as possible, and orally as soon as feasible. The perioperative initiation of extended-release transdermal or fast-onset transmucosal opioids to treat acute pain should be avoided.

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Research that extends well beyond the immediate postoperative period is needed. Brandal and colleagues[13] summarised the experiences of one institution in implementing opioid-sparing anaesthesia as part of an enhanced recovery plan in the operating room. Intraoperative opioid use was reduced, but the quantities of opioid medication given at the time of hospital discharge remained unchanged. Changing the analgesic plan in the operating room alone without adopting a comprehensive strategy that extends through recovery from surgery will decrease the effect of opioid-sparing strategies. Clarke and colleagues[14] describe their experience with a transitional pain service consisting of a multidisciplinary team of pain physicians, specialised nurses, and pain psychologists. A cohort of 250 Canadian patients (ranging from 19–81 years; 44·4% female), who had surgery and were at high risk of poor compliance with use of opioid analgesics after surgery, showed a marked reduction in opioid consumption and 26% of long-term opioid users were weaned of the drugs completely, without any negative effect on pain or physical function. Additionally, they saw a reduction in the length of hospital stay with an improvement in quality of life in those managed by the transitional pain service.

Education will need to include patients, hospitals, health-care systems, and the graduate schools where health-care providers are trained. By educating patients

about the risks and alternatives to opioids, health-care providers can help empower patients (and themselves) to request alternatives and demand closer attention if they are struggling after surgery. Opioid-free anaesthesia has been put forward as a panacea for the opioid problem, but there is no evidence that opioid-free anaesthesia is superior to multimodal analgesia.[15] For now, opioids remain an essential and reliable tool for treating moderate to severe pain.

Can we reduce or eliminate the transition from acute to chronic pain? Based on systematic reviews, there is preliminary evidence that regional anaesthesia can be protective against chronic postsurgical pain after thoracotomy and mastectomy,[16] and ketamine can decrease the risk of chronic postsurgical pain.[17] A wide range of demographic, genetic, clinical, perioperative, psychosocial, and psychophysical risk factors suggest that there might be no one single intervention that can protect all patients.[3] In the future, we believe standardised preoperative patient stratification will guide clinicians in designing an optimal and individualised analgesic plan.[18] That treatment plan should start preoperatively, integrate with the care provided in the operating room and during the course of hospitalisation, and be continued after hospital discharge until pain has subsided, in transitional pain clinics when necessary.[9]

The current debate around opioids calls for education and moderation. The authors of the new *Lancet* Series on postoperative pain management and opioids[3,6,9] are to be commended for their comprehensive account of opioids and their current use and misuse in perioperative pain management, for detailing strategies to reduce inappropriate prescribing, and for improving our understanding of the adverse effects and dangers of opioids. Each Series paper has pointed a way forward, and laid out how constructive change can be implemented on many levels from drug discovery to direct communication with patients, all the way to legislative action.

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Postoperative pain management and opioids 1

Transition from acute to chronic pain after surgery

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Over the past decade there has been an increasing reliance on strong opioids to treat acute and chronic pain, which has been associated with a rising epidemic of prescription opioid misuse, abuse, and overdose-related deaths. Deaths from prescription opioids have more than quadrupled in the USA since 1999, and this pattern is now occurring globally. Inappropriate opioid prescribing after surgery, particularly after discharge, is a major cause of this problem. Chronic postsurgical pain, occurring in approximately 10% of patients who have surgery, typically begins as acute postoperative pain that is difficult to control, but soon transitions into a persistent pain condition with neuropathic features that are unresponsive to opioids. Research into how and why this transition occurs has led to a stronger appreciation of opioid-induced hyperalgesia, use of more effective and safer opioid-sparing analgesic regimens, and non-pharmacological interventions for pain management. This Series provides an overview of the epidemiology and societal effect, basic science, and current recommendations for managing persistent postsurgical pain. We discuss the advances in the prevention of this transitional pain state, with the aim to promote safer analgesic regimens to better manage patients with acute and chronic pain.

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This is the first in a Series of three papers about postoperative pain management and opioids

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Introduction

Acute pain is almost ubiquitous after surgery. Fortunately, it can be controlled and mostly resolves within 1 week. It should not cause distress or limit postoperative recovery.[1] However, for some patients acute postoperative pain persists beyond the usual time of tissue healing and transitions into a chronic pain state.[2–6]

The prevalence of chronic postsurgical pain (CPSP), which is bad enough to cause substantial functional impairment, is approximately 10% after all surgeries (table 1).[6] Globally, more than 320 million people have surgery each year, which represents a vast potential for CPSP.[25] As a result, CPSP is increasingly recognised as a public health problem, not only because of the discomfort, distress, and disability it causes, but also because past approaches to managing it have contributed substantially to the current opioid crisis.[26] The use of opioids for atients who have surgery presents a particularly challenging problem requiring clinicians to balance two competing interests: managing acute pain in the immediate postoperative period and minimising the risks of persistent opioid use after surgery. Finding ways to minimise this risk is particularly salient in light of a growing literature suggesting that patients who have had surgery are at increased risk of chronic opioid use.[27] As a result, in 2016, the Joint Commission in the USA began a project to revise its pain standards and address the opioid epidemic.[26] In January, 2018, the Commission added an emphasis on the need to actively engage medical staff and hospital leaders to include strategies to decrease opioid use. This included the use of at least one of non-pharmacological modality for pain treatment and access to prescription drug monitoring programmes. There was also a stronger focus on pain assessments of how the pain affects patients' physical function.[28]

Postsurgical pain is a paradigm for understanding and studying other pain that is also iatrogenic.[29,30] Because CPSP occurs from a planned incision at a specified point in time, it has the potential to be prevented and better controlled. However, there are many factors that contribute to the development and persistence of CPSP, and only some of these are related to the surgery. As with non-surgical chronic pain, psychological and social factors have an important influence. All clinicians—not just surgeons and anaesthetists—should have some knowledge on CPSP and how to manage established cases, which can persist for months or years after the procedure. As with many other chronic conditions, early intervention is likely to improve outcomes and so identifying patients at risk is crucial.

Definition

CPSP is pain that occurs at the site of the incision or related areas of the surgery and persists a month longer than it takes for most injured tissues to fully heal. Consequently, the time of onset has mostly been set between 3 and 6 months.[22,31,32] Definitions of CPSP also vary as to whether or not other causes of pain, such as disease recurrence after surgery or presence of a pre-existing pain syndrome, are included under the CPSP rubric.[32] For example, chronic pain after lumbar spine surgery, also known as failed back surgery syndrome, refers to chronic back or leg pain that continues or recurs following spinal surgery, and affects more than 20% of patients.[16,33] The 11th revision of the International Classification of Diseases defines CPSP as pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, persisting beyond the healing process (ie, at least 3 months) and not better explained by another cause such as infection, malignancy, or a pre-existing pain condition.[34]

Clinical features

The nature of CPSP is often poorly characterised in clinical studies,[35] but aching is the most commonly chosen sensory descriptor of persistent pain after a range

	Any intensity (%)	Moderate-severe intensity (%)	Prevalence (%); prevalence if restricted to a severe pain rating	Number of operations in US non-federal community hospitals* in 2014[7]
Amputation of limb	30–85%	5–10%	Up to 85%[8]	Not available
Arthroplasty, knee	13–44%	15%	44% (15%)[9]	723 086
Caesarean section	6–55%	5–10%	Up to 12%[10]	1 142 680
Cholecystectomy	3–50%[11]	Not reported	Not reported	300 245
Craniotomy	0–65%[12]	25%	12–16%[13]	Not available
Hip replacement	27%	6%	27% (15%)[9]	487 625
Inguinal hernia repair	5–63%	2–4%	6–29%[14]	Not available
Laminectomy and spinal fusion	10–40%	4–6[15]	5–36% [16,17]	564 911
Mastectomy	11–57%	5–10%	22%[18]	Not available
Coronary artery bypass graft	30–50%	5–10%	28% (4%)[19]	160 240
Thoracotomy	5–65%	10%	48%[20,21]	Not available

*Non-federal community hospitals account for 786 874 (87%) of 902 202 hospital beds in the USA.

Table 1: **Prevalence of chronic postsurgical pain in common surgeries in the USA**[11,22–24]

of different surgical procedures.[9] Neuropathic descriptors such as hyperalgesia (heightened sensitivity to painful stimuli), dysaesthesia (an unpleasant, abnormal sense of touch), and allodynia (sensitivity to normally non-painful, often repetitive, stimulation) are frequently used. These descriptors suggest that nerve damage during the surgery is the cause, with the development of a sensitised central nervous system due to prolonged afferent traffic (eg, as a result of ongoing inflammation arising from an implant or due to wound infection).[36] It now appears that both peripheral and central sensitisation occur after an incision, with central sensitisation occurring in both the spinal cord and the brain, and unique mechanisms are involved that might yield novel drug targets.[37] In a survey 3–4 years after surgery, neuropathic descriptors were used less commonly after hip (1%) and knee replacement surgery (6%),[38] suggesting that other pain-generating mechanisms are involved.

A common feature of CPSP is that the painful sensations change from the familiar acute postoperative pain that is injury related and wound focused to a complex, multifaceted pain syndrome that can increase in intensity in the days, weeks, and then months after the surgical procedure.[39] Because CPSP also commonly occurs following surgeries for cancer, the possibility of local recurrence needs to be kept in mind.[40] Like other chronic pain, CPSP rarely occurs in isolation but clusters with other symptoms, including pain-related interference with mood (28%), sleep (30%), and enjoyment of life (30%).[41] Psychological factors are also consistently associated with CPSP, including anxiety, depression, pain catastrophising, and general psychological distress.

Epidemiology: incidence and prevalence

The definitional issues related to chronology and whether recurrence of pre-existing pain is included have hampered definitively establishing the true incidence and prevalence of CPSP. Methodological issues related to data collection have also contributed to this situation. Most studies report on data collected in a single institution or at a national level but this can be problematic, for different reasons.[42] Single institution studies use patient-based data from the perioperative period, are often limited to one specific type of surgery, and include only small samples.[43] Nationwide studies have followed large samples of patients, but have mostly collected retrospective data and therefore are of doubtful general validity. To improve our understanding of the incidence of CPSP and the associated risk factors, large prospective international studies that use standardised methods to record surgical and other perioperative characteristics, including analgesic use, are needed. Because pain is both a sensory and an emotional experience, psychological factors such as mood, disability and pain coping (eg, pain self-efficacy and pain catastrophising) should also be measured using validated standardised questionnaires. Ethnic, cultural, and linguistic differences in expressing pain and distress might need to be stratified for in an international survey, but how these factors interact with other psychosocial issues is not well understood.[44]

Notwithstanding these limitations, the extent of the problem of CPSP has been increasingly recognised over the past two decades. A report, published in 1998, described 5130 patients who attended ten outpatient pain clinics in the UK, and found that CPSP was present in almost one in four patients.[45] A cross-sectional survey of all adults living in Tromso, Norway (population 75 000), found that 826 (40%) of 2043 patients who recalled having had surgery between 3 and 36 months ago reported ongoing pain in the operated area.[46] This study also revealed that CPSP accounted for approximately a third of chronic pain cases in the community. However, other studies have indicated that CPSP is less common, affecting approximately 10% of people at 1 year after major surgery,[2,3,47,48] and is intolerable in 1%.[49] In a Portuguese cross-sectional epidemiological study, only 91 (6%) of 2213 patients with chronic pain attributed its cause to surgery.[50] It has been estimated that 20% of children experience CPSP 1 year after surgery.[51] Although its exact incidence is unknown, CPSP is far more common than most other postsurgical complications and has long-term consequences. The health-care resource implications of CPSP should not be underestimated.

CPSP has been reported after almost all types of surgery, with a high prevalence (>20%) reported after thoracic, breast, inguinal hernia, lumbar spine, and hip or knee arthroplasty surgery (table 1).[4,16,33,52–54] Persistent pain is also common after surgery for trauma and burns surgery.[55,56] The reason for the high prevalence of CPSP after these procedures has been attributed to the increased risk of nerve injury,[4] but there could be other explanations, including not only central sensitisation,[37] but also continuation of pre-existing pain in the operated area.[57]

Furthermore, CPSP follows minor surgeries, despite evolution in surgical techniques. For example, introduction of minimally invasive approaches such as laparoscopy have only slightly reduced the prevalence of CPSP.[35,58]

Natural history and prognosis of CPSP

Without large, long-term, prospective studies, the natural history and prognosis of CPSP is hard to predict. On the basis of data in table 1 CPSP does appear to often resolve by the end of the first year. In one study,[42] the syndrome was reported to be present 12 months after surgery in 315 (14%) of 3120 patients, being moderate in 12% and severe in 2%. In the aforementioned Tromso study,[46] 40% of patients reported CPSP an average of 18 months after surgery, and 18% rated it as moderate or severe. Studies[44] in children have identified several postoperative pain trajectories. Acute postoperative pain got better, worse, or stayed the same; and 10% of children with little or no pain initially had moderate to severe pain up to 5 years later.[59]

Mechanisms of transition from acute to CPSP

Some molecular mechanisms responsible for the transition of acute to chronic pain and their neurobiological correlates have been identified in animal models of chronic pain.[60–65] The sensory aspects of pain are carried by a bidirectional network of neurons that transmits a variety of noxious signals from peripheral nociceptive Aδ-fibres and C-fibres to the dorsal horn of the spinal cord (SCDH). Here, noxious signals are passed to ascending projection neurons that convey them to the cortex via the thalamus. Noxious signals are modulated and shaped at every level of the nervous system, including powerful descending pain pathways (figure 1). More complete reviews of the mechanisms that contribute to chronic pain are available.[63,65–67]

Nociceptive afferents and the SCDH

Tissue damage during surgery plays a definitive role in the development of CPSP, and triggers profound changes in peripheral and central somatosensory circuits. Nociceptive inputs into the SCDH release the neurotransmitter glutamate, which acts at specific receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors and the frequently implicated N-methyl-D-aspartate receptors (NMDARs).[68] Following nerve injury, nociceptive neurons fire rapidly leading to changes in NMDAR composition and activation. NMDARs are highly permeable to calcium, whose influx triggers neuron-specific cascades that underlie synaptic plasticity and, in extreme cases, cause excitotoxicity and neuronal death.[69] In a neuropathic pain model, the conditional deletion of spinal NMDARs prevents calcium-dependent neuronal death and the transition from acute to persistent pain-like behaviours. This shows that glutamate, NMDARs, and calcium influx play an essential role in the development of chronic pain.[69] Multiple studies[70–74] that have inhibited NMDAR or voltage-gated calcium channels (eg, the gabapentinoids) preoperatively or perioperatively to try to prevent CPSP, and reduce opiate use after surgery have had mixed success. Diverse outcomes are likely related to innate differences in surgeries, and psychosocial risk factors. Additionally, the inhibitors used are not highly specific for pain circuits or their target proteins. More consistent results, with fewer side-effects, might result from targeted drug delivery to nociceptive neurons during surgery.

A promising strategy, which could be used during surgery, is to interfere with the messenger RNA mediated cascade of pain-induced protein synthesis that occurs following injury. This is achieved by injecting a highly stable decoy RNA-binding protein into the site of injury at the time of injury. This strategy has been tested in a variety of mouse models of inflammatory sensitisation, and the decoy RNA-binding protein reduced the behavioural correlates of central sensitisation and increased the rate of recovery from sensitisation in the hours and days following the inflammatory challenge.[75]

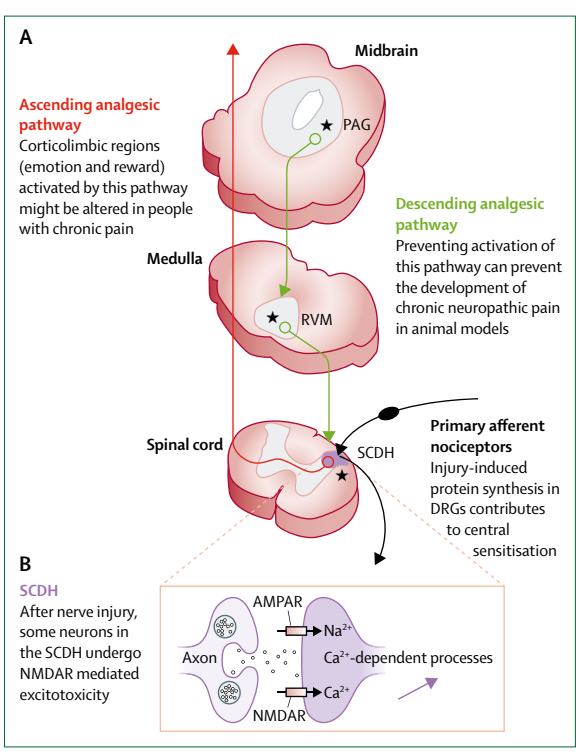

Figure 1: Neural pathways for pain
Fundamental changes to neuronal phenotypes and brain circuits occur when pain becomes chronic. These changes can alter sensory, emotional, and motivational centres of the brain and interfere with the action of traditional analgesic medications. A complete understanding of how these circuits work in acute and chronic pain is needed before we can prevent or treat chronic pain. (A) Schematic diagram of the ascending and descending pain pathways showing treatment possibilities. Injecting tetrahydrocannabinol or cannabidiol into the PAG, RVM, or SCDH is analgesic in animal models of neuropathic pain (stars). (B) A glutamate releasing synapse with calcium permeable NMDA receptors. AMPAR=α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors. Ca^{2+}=calcium. DRG=dorsal root ganglia. Na^{2+}=sodium. NMDAR=N-methyl-D-aspartate receptors. PAG=periaqueductal grey. RVM=rostral ventromedial medulla. SCDH=dorsal horn of the spinal cord.

	Subgroup with worse CPSP	Consistency of evidence	Timing of data collection		
			Preoperative	Intraoperative	Postoperative
Demographic					
Age	Younger adults	Consistent	+	..	..
Gender	Female	Mixed	+	..	..
Marital status or living arrangements	Single or living alone	Mixed	+	..	..
Education level	Less educated	Consistent	..	..	..
Employment status	Unemployed	Mixed	..	..	..
Compensation status	Seeking compensation	Consistent	..	..	..
Lifestyle	Smokers	Consistent	..	..	..
Gene mutations	Various single gene candidates (eg, *COMT*, *OPRM1*, *GCH1*)	Few data	+/–	..	..
Clinical					
Medical comorbidities	More	Consistent	+	..	..
Body-mass index	Higher	Mixed	+	..	..
Prior disability	Greater	Consistent	+	..	..
Surgery related					
Duration of surgery	Longer	Consistent	..	+	..
Surgical technique	Nerve injury	Mixed	..	+	..
Analgesia regimen	Systemic, reactive *vs* spinal, pre-emptive	Mixed	+	+	..
Anaesthesia	General *vs* regional	Mixed	..	+	..
Complications	More	Consistent	..	+	+
Pain					
Preoperative	Present	Consistent	..	..	..
Postoperative, intensity	Stronger	Consistent	+	+	+
Postoperative, duration	>5 days	Consistent	+	+	+
Psychological					
Fear or anxiety	Greater	Consistent	+	..	+
Depression	Greater	Consistent	+	..	+
Pain catastrophising	Greater	Consistent	+	..	+
Other psychological issues (eg, vulnerability factors)	Present	Few data	..	..	..
Physical functioning					
Pain interference	Worse	Consistent	+	..	+

CPSP=chronic postsurgical pain. *COMT*=catechol-O-methyltransferase. *OPRM1*=opioid receptor mu 1. *GCH1*=guanosine-5′-triphosphate cyclohydrolase 1. + appropriate timing of data collection. +/–The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials expert panel acknowledged that many studies of CPSP might not be designed or have sufficient power to test genetic hypotheses. In these cases, collection and storage of biological samples for future genotyping is strongly recommended.

Table 2: **Proposed domains, constructs, and timing of data collection in future studies of chronic postsurgical pain**[23,104,105]

Cannabinoids

Cannabinoids, including the two predominant constituents of marijuana tetrahydrocannabinol and cannabidiol, modulate nociceptive signals[76] and might have a role in the treatment of CPSP.[77] The few clinical trials[78,79] that have overcome the ongoing legal barriers to doing human trials on cannabinoids in chronic pain have not identified a major analgesic advantage, although consistent improvements in sleep and mood have been reported. Animal data indicate that cannabinoids have efficacy for neuropathic pain;[80–83] however, there is a scarcity of firm clinical data. Additionally, synergistic pain relief has been reported with low doses of tetrahydrocannabinol and cannabidiol,[81,84] and with cannabinoids and morphine.[85] Therefore, combination cannabinoid therapies could effectively prevent acute postoperative pain in surgical patients with a high risk of nerve damage, but there remains some concern about their side-effects.[86]

Descending modulation

The most studied descending pain pathway projects from the midbrain periaqueductal grey (PAG) to the rostral ventromedial medulla (RVM), which sends inputs directly onto nociceptive neurons in the SCDH.[87] This pathway has the ability to strongly influence the pain experience; for example, electrical stimulation of the PAG blocks spinal responses to noxious stimuli, and simulation of the RVM can both inhibit and facilitate pain signals.[88] This descending pathway plays an essential role in the development of chronic pain following nerve damage, because lesions to the site where descending pain fibres enter the spinal cord can prevent the development of neuropathic pain in animal models,[87,89–95] which suggests that avoiding PAG-RVM involvement during some period after surgery could reduce the incidence of CPSP.[64] An animal study that used genetic technologies found that selective activation of a subset of RVM neurons that release γ-aminobutyric-acid increased responses to mechanical stimulation (hyperalgesia) without changing responses to thermal stimuli. By contrast, turning off these same neurons reduced mechanical responses (hypoalgesia) and when animals were subjected to long periods of stress, these neurons were activated and mechanical hypersensitivity was enhanced.[96,97] The study shows that just one small descending circuit can set pain thresholds, and inhibit and facilitate responses to noxious mechanical stimulus. Additionally, this circuit responds differently to long and short periods of stress and might be part of a mechanism that explains why patients with pre-existing stress have a higher risk of developing CPSP.

Behavioural correlates

Neuroimaging in humans has shown that brain regions associated with emotions and motivation are activated during noxious stimulation and these regions can be altered in structure, activity, or connectivity in patients with chronic pain.[62] A study[89,99] that followed up patients with acute back pain for 3 years found that the anatomical characteristics of corticolimbic circuitry (responsible for emotion and reward) are the dominant predictor (60% of the variance) for patients who developed chronic pain. This finding suggests that associative circuits are more important than pain-related ones for the development of chronic pain and thus should be the major focus

of research and therapeutic interventions.[100] Addictive substances such as opioids alter the plasticity of the corticolimbic circuits, and conversely, persistent pain promotes opiate reward.[101] The increase in opiate reward measured in mice with neuropathic pain was specifically dependent on signalling changes in a group of cortico-limbic neurons that contain the peptide hormone corticotropin-releasing factor. This finding mechanistically links synaptic plasticity induced by chronic pain to behavioural susceptibility to increased opiate reward[102] and suggests that therapeutic strategies that seek to normalise corticolimbic connectivity could improve chronic pain and opiate use outcomes.

Our neurobiological understanding of pain suggests that noxious signals are integrated by multiple distinct and overlapping neuronal populations and brain regions. Researchers are only just beginning to unravel these complex circuits and interactions to understand when and how they shape and scale sensory input and how their relative contributions affect the experience of pain.[103] Because of the various factors that can contribute to the development of chronic pain, a single treatment is unlikely to be effective and appropriate for all patients with chronic pain. CPSP has an advantage from a research perspective of occurring in response to a known injury. Biomedical and psychological testing before and after the nociceptive challenge can be assessed and potential therapeutic compounds could be locally delivered to the site of injury before and during surgery.

Predictors of CPSP

The ability to predict who is at risk of developing CPSP is clearly important, especially if the risk factors are modifiable. Despite the progress in understanding the transition from acute to chronic pain, the research to date mainly identifies clinical risk factors. This literature is summarised in table 2. To facilitate future research in this field, a standardised approach to data collection of patient-reported and clinical outcomes has been proposed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and is outlined in panel 1.[104] Five core risk factor domains have been identified: demographic, genetic, clinical, surgery related, and psychological. Four outcome domains have been identified, with standardised validated tools for measuring them: pain, physical functioning, psychological functioning, and global rating of outcome. Standardisation of the definition of CPSP and uniformity in the timing of follow-up to assess transition from acute to chronic pain at multiple timepoints are other methodological issues that have been emphasised in this Series.

Risk factors for CPSP are not independent of each other, but interlinked.[23] For example, preoperative chronic pain is more common in women, and sensitivity to experimental pain stimuli is often accompanied by mood disorders such as depression and anxiety. It is therefore not surprising that patients with established chronic pain and pain-related behaviours are more likely to report increased acute postoperative pain that is often difficult to treat because of tolerance and opioid-induced hyperalgesia from their previous treatment of chronic pain with high-dose opioids.

Panel 1: **Risk factors for chronic postsurgical pain**

Demographics and lifestyle
- Age
- Gender
- Marital status or living arrangements
- Education level
- Employment status
- Compensation status
- Obesity
- Smoking

Genetic
- Candidate gene mutations associated with increased pain (eg, *COMT*,*OPRM1*, and *GCH1*)

Clinical
- Surgical factors, including surgical technique (open *vs* laparoscopic), duration of surgery, type of anaesthesia (general *vs* regional), and perioperative
- Analgesic regimen (systemic *vs* spinal and pre-emptive); surgical complications and re-operating
- Medical comorbidities
- Previous disability or pain interference

Preoperative pain (area of operation or elsewhere)

Postoperative pain (intensity and duration)

Psychological
- Fear or anxiety
- Depression
- Pain catastrophising
- Other psychological issues (eg, vulnerability factors)

COMT=catechol-o-methyltransferase. *OPRM1*=opioid receptor mu 1. *GCH1*=guanosine-5′-triphosphate cyclohydrolase 1.

Predictive tools

Because there are multiple, interacting risk factors for developing CPSP, attempts have been made to develop predictive tools that quantify the level of composite risk. Most have been operation specific, but one generic tool evaluated the effect of 14 biomedical and psychosocial items that were derived from a systematic review of the CPSP risk factor literature.[106] From a training set of 150 patients, of whom almost half developed CPSP, five of the 14 items were independently predictive of developing CPSP, of which four are assessable preoperatively (pain in the surgical field, comorbid chronic pain at other sites, capacity overload, and comorbid stress) and one postoperatively (moderate to severe postoperative pain persisting at day 5). Because the five risk factors were of similar importance (odds ratios all approximately 2–3),

***Panel 2*: Design issues for studies evaluating interventions that aim to prevent the development of transitional and chronic postsurgical pain[105]**

Patient population
- Initial focus on surgeries with high likelihood of chronic postsurgical pain (eg, amputation, mastectomy, thoracotomy, and herniorrhaphy)
- Ideally surgeries for painful conditions, or in sites of pre-existing pain
- If intervention is effective, broaden focus to other surgical populations

Risk factors
- Need to be adjusted and stratified for (see table 2)

Timing of preventive intervention
- Commence treatment early enough (eg, sometimes weeks before surgery)
- Continue for duration of acute postoperative pain and the transitional phase, if possible and feasible

Outcome measure
- Consider how pain presence, intensity, quality, and aggravating factors will be measured

Timing of endpoint
- First outcome score (eg, at 1, 2, or 3 months postoperatively)—depends on type of surgery
- Specify duration of data collection—quarterly for at least 12 months is recommended
- Measure amount and type of acute postoperative pain
- Design of follow-up studies influenced by effect of the intervention on acute postsurgical pain

they were each given the same rating to ease scoring in routine clinical use. Patients with three to five positive risk factors were more likely to go on to develop CPSP than were those with zero to two factors (sensitivity 74%, specificity of 65%). However, as yet no validation studies by the authors or other reports of clinical use of the tool have been published.

For specific surgeries, tools have been developed for predicting chronic post-herniorrhaphy pain and persistent pain after breast cancer surgery.[107,108] The hernia surgery tool utilises just two preoperative factors: pain-related impairment score and pain intensity score in response to a tonic heat stimulus of 47°C.[107] It had fair predictive and discriminatory ability. The authors suggested to use this approach to direct patients at high risk (severe preoperative impairment and high preoperative pain sensitivity) of CPSP away from open surgery (70% risk) to laparoscopic hernia repair (30% risk). However, this tool has not been widely used nor further validated.

The tool for predicting persistent pain after breast cancer surgery was developed in a training set of 860 patients in Finland and consists of five factors: high body-mass index, preoperative pain in the operative area, axillary lymph node dissection, maximum pain intensity on the first day, and maximum pain intensity on the seventh day.[93] It was validated in two independent test sets from Denmark and Scotland. 13·5% of the participants had moderate to severe persistent pain in the first study, 13·9% in the second study, and 20·3% in the third study. The model performed well in predicting persistent pain with 74% accuracy in the two test sets. At the 20% risk level, the model had 33% sensitivity and 94% specificity in the Danish cohort and 47% sensitivity and 82% in the Scottish cohort. Data points can be collected at day 7 if recall of preoperative pain is accepted, and an online risk calculator is available.

Prevention of transitional postsurgical pain and CPSP

Some CPSP risk factors are modifiable (eg, body-mass index, preoperative pain, and some comorbidities), especially if surgery is elective, whereas others (eg, demographics, genetics, and pain sensitivity) are not. The very name of CPSP implies the pain is caused by surgery and therefore can be controlled if not prevented.[109] Intraoperative nerve injury is a probable contributor to the development of at least some CPSP, but few studies have assessed whether intraoperative nerve handling or elective preservation or division of major sensory nerves contributes to the development of chronic pain or numbness,[110] therefore the results are inconclusive.[23] Anaesthetic technique could also be important, particularly avoiding high-dose exposure to the short-acting opioid remifentanil.[111,112]

Optimising perioperative pain management should reduce the incidence of CPSP; however, evidence remains elusive, with most pharmacological interventions being unhelpful in preventing CPSP.[111–113] Studies of local and regional anaesthesia, non-opioid analgesics such as non-steroidal anti-inflammatory drugs, NMDA-receptor antagonists, and antiepileptic and antidepressant drugs have generally been disappointing.[114,115] Long-term follow-up studies of two large randomised trials (ENIGMA[116] and ENIGMA-II)[116] that evaluated nitrous oxide for anaesthesia found some evidence that nitrous oxide prevents CPSP in Chinese patients and those with variants in the methylene tetrahydrofolate reductase gene.[2,47] This finding supports a possible genetic contribution to longer-term effects of nitrous oxide in the prevention of CPSP.

In addition to the clarification of the definition of CPSP, there has been a focus on optimising the design of studies evaluating interventions aiming to prevent the development of transitional and chronic postsurgical pain (panel 2).[105]

Potential role of a transitional pain clinic

A more pragmatic approach to prevention of CPSP has been the development of transitional pain clinics, which aim to overcome the disconnect between ward-based acute postoperative pain management and outpatient chronic pain management (figure 2). Such a comprehensive and integrated pain service can identify patients at risk of chronic pain through inpatient screening on the basis of established prognostic indicators.[3,4,6,33,39,54,55,1117–120] A further clinic visit of at-risk patients at 6–12 weeks after discharge from hospital can review treatments and liaise with the patient's general practitioner. Referral to other services can include rehabilitation, mental health services,

addiction medicine, and multidisciplinary chronic pain services in addition to ongoing surgical reviews.[48] This should modify the pain trajectories of patients who are at an increased risk of excessive opioid consumption and CPSP.[121] A transitional pain clinic will also allow for earlier targeted interventions. Cost-effectiveness is supported by the likely savings on medical and other treatment costs, unplanned readmissions, and reduced long-term disability and failure to return to work. Such a model of care would offer better support for the patient, their family, and community health-care providers. This model could reduce opioid use and rates of opioid abuse. It would also be a source for research, audit, training, and education into the future management of CPSP.

The Transitional Pain Service at Toronto General Hospital has reported on their three-stage approach to reducing CPSP and the need for opioid medications: preoperatively, postoperatively (but in hospital), and postoperatively (outpatient setting) for up to 6 months after surgery.[5,48] Of their first 200 consecutive patients presenting for elective major surgery, they identified 51 who reported a preoperative chronic pain condition, with 12 (24%) taking opioid medications before their surgery.[5,48] At 3 months after surgery, 70 (35%) patients in their cohort reported having surgical wound pain and 27 (14%) continued to use opioids for postoperative pain relief.

In Finland, an acute pain service-outpatient clinic is used by different surgical specialties to follow up patients at risk of CPSP, the two most common specialties being thoracic and orthopaedic surgery.[122] Their results suggest a large unmet need in most hospitals around the world: 139 (70%) of 200 had symptoms indicating neuropathic postsurgical pain. The patients had an average of five risk factors for CPSP. The median time from surgery to the first contact to the acute pain service-outpatient clinic was 2 months, and the median duration of follow-up was 2·8 months (range 0–16 months). The median number of contacts with the clinic was three (range one to 14); 25% needed only one visit to the clinic, 19% had an appointment with the physiotherapist, and 20% with a psychologist or psychiatrist. At hospital discharge after surgery, 54% of the patients were using weak opioids, 32% strong opioids, and 71% gabapentinoids; at discharge from the clinic, these proportions were 20%, 6%, and 43%, respectively. 22% were referred to the multidisciplinary pain clinic for further pain management.[122]

Treatment of established CPSP

In a review of CPSP in 2006, numerous potential symptomatic targets were proposed.[22] The main two targets for which success has been achieved are the α_2 and δ-1 subunit of calcium channels by gabapentin and pregabalin, and the monoamine transporters (which augment descending inhibition) by serotonin norepinephrine reuptake inhibitors such as duloxetine and venlafaxine.[123,124] These drugs are widely used for chronic neuropathic pain but their effects are variable, with the number needed to treat ranging from six to eight.[125] More research needs to be done to understand which subgroups of patients with CPSP are most likely to benefit.

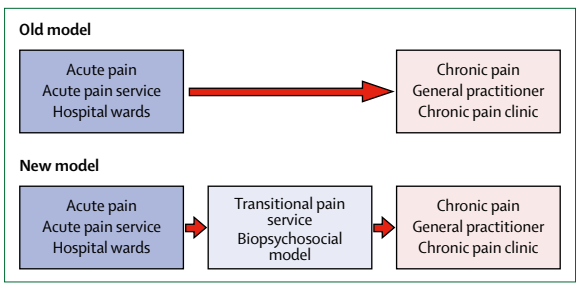

Figure 2: **A transitional pain clinic model**
Care in hospital and after discharge pathways.

Of the other target inhibitors listed in the review, ziconotide is an N-type calcium channel Cav2·2 blocker that is clinically effective as an analgesic but is rarely used because it requires intrathecal administration and has a narrow therapeutic window.[126] Despite these limitations, calcium channel modulation remains a target of interest in chronic pain control.[127] Sodium valproate could be effective in neuropathic pain; findings from an animal model showed that this effect is achieved via upregulation of glutamate transporters and enhances the analgesic effects of riluzole, a glutamate transporter activator.[128] Inhibitors of voltage-gated sodium channels have been developed and are being evaluated in early-phase clinical trials.[129] Other targets mentioned that are still in preclinical study include potassium channel openers on sensory neurons,[130] P2X4 and P2X7 purinergic receptor antagonists on glial cells,[131] and caspase inhibitors.[132] It has recently been shown that caspase inhibition might be one of the mechanisms of action of non-steroidal anti-inflammatory drugs.[133]

Our understanding of the neuropharmacology of the somatosensory pathways and associated structures (eg, glial cells) has grown since 2006, and new targets have been established. Novel opioids, alpha-adrenergic agonists, oxytocin, and cannabinoids are the targets of interest.[36] Although these agents hold promise, the experience with the gabapentinoids, serotonin, and noradrenaline reuptake inhibitors is that loosely targeted pharmacological strategies are unlikely to successfully combat the complex problem presented by chronic pain. Novel approaches including target toxins, gene-based approaches such as protein synthesis blockade and transfection, and deep brain stimulation[36,75,134] might be useful.

On the one hand, CPSP with strong neuropathic components might also be amenable to interventional techniques such as radiofrequency ablation of local sensory nerves or neuromodulation; however, no conclusive recommendations can be made because of the poor quality of available data.[40] On the other hand, psychosocial risk factors for CPSP have been consistently

identified, and multidisciplinary pain management programmes with psychological approaches including cognitive behavioural therapy or acceptance and commitment therapy have shown encouraging results in the management of CPSP.[135,136] The National Institute for Health and Care Excellence recommends an individualised treatment plan with regular reviews for patients with neuropathic pain.[115]

Conclusions

CPSP is a growing problem as the population ages and more surgeries are done. Poorly controlled acute postoperative pain is a predictor of CPSP development but the drugs currently available to treat acute pain are mostly ineffective at preventing it. Opioids are too often overused, particularly in the post-discharge period. Preclinical research might yield new drug treatments, but ultimately, CPSP is similar to other chronic pain and therefore requires a comprehensive biopsychosocial approach to treatment. Transitional pain clinics are a new approach at bridging the divide, with elimination of overprescribing of opioids after surgery being a major goal.[122,137]

Contributors

All authors contributed equally to the content of the manuscript and approved the final version.

Declaration of interests

The authors declare no competing interests.

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Postoperative pain management and opioids 2

Inappropriate opioid prescription after surgery

Mark D Neuman, Brian T Bateman, Hannah Wunsch

Worldwide, the use of prescription opioid analgesics more than doubled between 2001 and 2013, with several countries, including the USA, Canada, and Australia, experiencing epidemics of opioid misuse and abuse over this period. In this context, excessive prescribing of opioids for pain treatment after surgery has been recognised as an important concern for public health and a potential contributor to patterns of opioid misuse and related harm. In the second paper in this Series we review the evolution of prescription opioid use for pain treatment after surgery in the USA, Canada, and other countries. We summarise evidence on the extent of opioid overprescribing after surgery and its potential association with subsequent opioid misuse, diversion, and the development of opioid use disorder. We discuss evidence on patient, physician, and system-level predictors of excessive prescribing after surgery, and summarise recent work on clinical and policy efforts to reduce such prescribing while ensuring adequate pain control.

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This is the second in a Series of three papers about postoperative pain management and opioids

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Introduction

Worldwide, the use of prescription opioid analgesics more than doubled between 2001 and 2013.[1] In some countries, including the USA,[2] Canada,[3] Australia,[4] and the UK[5,6] the growth of prescription opioid dispensing over time has been linked to increases in harm related to opioid misuse and abuse.

The common prescribing of opioids for pain treatment after surgery has prompted efforts to balance the desire to achieve adequate postoperative pain control and mitigate opioid related adverse events. Although decreasing the use of opioids for postoperative pain management has been a longstanding theme in the anaesthetic and surgical literature,[7] recent work has found that patients in some countries frequently receive opioids either unnecessarily or in excess of their requirements for surgical pain control.[8] Such work, combined with findings that prescription opioids could be commonly misused,[9] and that initiation of illicit opioid use is frequently preceded by prescription opioid misuse[10–12] has made efforts to reduce opioid prescribing after surgery a major priority for clinical care and health policy in multiple countries.

In this second paper in this Series, we review evidence on the evolution of prescription opioid use for pain treatment after surgery in the USA, Canada, and other countries, and focus in particular on prescribing practices after discharge. We summarise evidence on the extent and potential consequences of excessive postoperative opioid prescribing for individual patients and public health more broadly. Next, we review available evidence on system, physician, and patient-level predictors of excessive opioid use after surgery; finally, we summarise recent work on clinical and policy initiatives to reduce excessive opioid prescribing among patients who undergo surgery.

Historical context

The history of the US opioid epidemic has been described in detail before.[13,14] In summary, between the mid 1990s and early 2000s, physicians, researchers, professional societies, government organisations, and accrediting bodies took steps to show that inadequate pain treatment was a key gap in the quality of health care in the USA.[15,16] In 1995, the American Pain Society introduced the Pain As The Fifth Vital Sign campaign, which encouraged clinicians and health systems to expand pain treatments, including through broader use of opioid analgesics.[17] The US Veteran's Health Administration[18] subsequently adopted this campaign, and in 2001 the Joint Commission,[19] which accredits US hospitals, published pain management standards that were highly aligned with aspects of the campaign. Joint Commission materials at the time cited consideration of the campaign as an example of positive implementation, and encouraged routine use of quantitative pain measurements to guide pain treatment for patients in hospitals.[19,20] Simultaneously, pain treatment advocates cited methodologically weak but frequently referenced studies[21,22] to argue that opioids were not addictive if used as directed[15,23] and advocated against "unnecessary withholding of opioid medications".[24] Such efforts were reinforced by policy efforts in the USA to link patients' ratings of pain intensity to hospital reimbursement through Medicare's Hospital Value Based Purchasing Programme.[25] Extensive marketing efforts by US pharmaceutical companies sought to downplay the risks of opioid treatment through aggressive marketing efforts, some of which have since become the focus of lawsuits in both Canada[26] and the USA.[27]

Global trends in opioid prescribing over time

According to data from the International Narcotics Control Board, global opioid analgesic use more than doubled between 2001 and 2013, from approximately 3 billion daily opioid doses per year to over 7·3 billion daily doses.[1] Notably, this growth in use was not uniformly distributed across the globe; while countries located in North America, western and central Europe, and Oceana experienced two-fold to three-fold increases in prescription opioid use over this period, countries in other regions experienced no substantial increases.

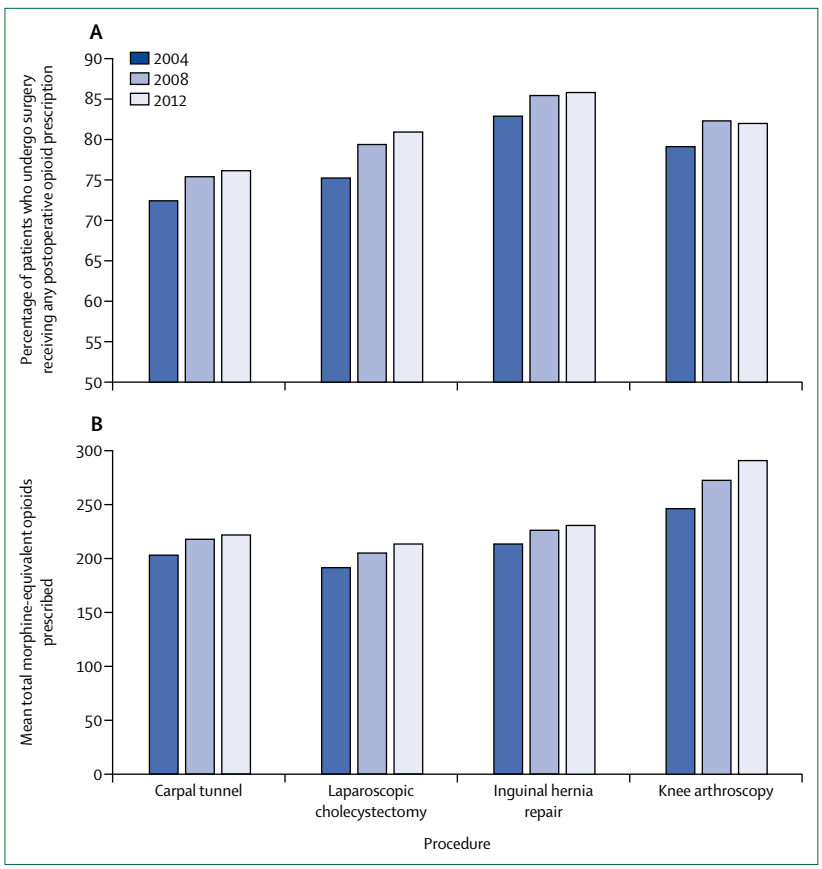

Figure: **Increasing prescribing of opioids after surgery in the USA**
Changes in patterns of postoperative opioid prescribing between 2002 and 2012 for four common low-risk procedures among 155 297 US adults who had private insurance and did not use opioids 6 months before surgery. (A) The percentage of all patients filling any opioid prescription within the first 7 days after surgery by year and procedure type. (B) The average amount of opioid pain medication received in morphine equivalents among those filling a prescription by year and procedure type.[44]

Nonetheless, as change occurs over time in factors hypothesised to underlie such international variation in opioid prescribing, such as differences in provider training; concerns regarding the risk of opioid dependence; local availability of opioid medications; and cultural attitudes towards pain management, growth in opioid prescribing in nations with historically low rates of use could create new challenges for public health to balance the potential benefits of such medications.[28] For example, Krawczyk and colleagues[29] examined pharmacy dispensing data from Brazil between 2009 and 2015, and found a greater than four-fold increase in opioid sales over this interval, along with an 11-fold relative increase in oxycodone sales. Similarly, in China, a Good Pain Management programme launched in 2011, with the goal of improving cancer pain treatment, has markedly increased the use of strong opioids in such contexts,[30] potentially improving the quality of palliative care; at the same time, placed alongside the US opioid epidemic, decreasing stigma surrounding opioid use and growth in opioid marketing efforts in China,[31] highlight the ongoing challenge of balancing access to effective pain treatment against risks of opioid overuse in diverse contexts across the globe.

Outpatient opioid prescribing after surgical procedures

Variability in prescribing

The predictors and pathophysiology of acute postoperative pain, the relationship between postoperative pain and phenomena such as acute opioid-induced hyperalgesia and persistent postsurgical pain, and the role of opioid and non-opioid strategies for pain management in the immediate (in-hospital) postoperative setting have been reviewed extensively elsewhere.[32–34] Here, we focus primarily on patterns of outpatient opioid prescribing after surgery (ie, among patients undergoing ambulatory surgery or after hospital discharge for inpatients who undergo surgery).

Few studies to date have compared opioid prescribing practices after surgery across countries; however, available evidence suggests marked international differences in patterns of opioid prescribing for individuals undergoing similar procedures. In 2009, Lindenhovius and colleagues[35] compared postoperative prescribing practices for patients who underwent surgery in one US hospital with patients in a hospital in the Netherlands. The authors found that 77% of patients undergoing hip fracture repair in the US hospital received opioids, whereas none did in the Netherlands hospital; 82% of US patients received opioids after undergoing ankle fracture repair versus 6% of Dutch patients. Similarly, a comparison of patients undergoing head and neck surgery at one US hospital versus a hospital in Hong Kong found that 87% of patients in the USA received opioid orders after surgery versus less than 1% of patients in Hong Kong.[36] Comparison studies highlight persistent differences between the USA and other countries in patterns of acute opioid prescribing; physician surveys assessing approaches to acute pain management in the USA compared with Japan,[37] France,[38] and the Dominican Republic[39] have shown that reliance on opioids for acute pain management is greater in the USA than in other settings. While few data are available to elucidate the reasons for such cross-national differences, it is likely that similar factors to those identified as influencing international patterns of opioid prescribing, such as differences in provider training, concerns regarding opioid dependence and diversion, and cultural attitudes towards pain management, are also likely to explain differences in postoperative opioid prescribing for specific procedures.[40,41] Although little is known regarding international differences in actual pain experiences after surgery, available data suggest that country of treatment accounts for a negligible amount of variation in early (postoperative day 1) measures of satisfaction with pain treatment after accounting for patient-level and hospital-level effects.[42] In a survey regarding satisfaction with

overall management of postoperative pain, satisfaction was highly related to impressions of improvement and appropriateness of care, as well as participation in pain treatment decisions.[42]

Unnecessary prescribing

Studies[8] suggest that opioid prescribing among US patients who undergo surgery can frequently be in excess of what is needed for pain control, with many receiving opioids that are not needed at all for adequate pain relief. Among 642 patients undergoing one of five outpatient surgeries at a US academic medical centre in 2015, Hill and colleagues[43] observed that 90·5% of patients received an opioid prescription at discharge, with substantial variation in the number of pills prescribed for a given procedure; for example, among patients undergoing open inguinal hernia repair, the number of pills prescribed ranged from 15 to 120. A review of six studies published between 2011 and 2017, showed further evidence of widespread overprescribing of opioids among US patients who undergo surgery; Bicket and colleagues[8] found that the proportion of patients reporting unused opioid tablets after surgery ranged from 67% to 92% across studies, with the overall proportion of unused tablets ranging from 42% to 71%.

Within the USA, studies on low-risk outpatients after surgery suggest that the amount of opioid dispensed for outpatient pain treatment after surgery has increased over time, even in the context of high baseline rates of opioid prescribing. In a national sample of US patients undergoing four low-risk surgical procedures (carpal tunnel repair, knee arthroscopy, laparoscopic cholecystectomy, and laparoscopic appendectomy), the percentage of patients who filled an opioid prescription after surgery increased from 2004 to 2012 for each procedure (figure). Although these data do not specifically show the causes of changes over time in postoperative prescribing, the average daily dose of opioid prescribed for postoperative pain increased by 13% across all procedures, with increases ranging from 8% for patients undergoing inguinal hernia repair to 18% for patients undergoing knee arthroscopy (figure).[44] More recent data have shown decreases in the amount of opioids dispensed per capita in the USA between 2010 and 2015,[45] which raises the possibility that earlier trends towards progressively higher rates of opioid utilisation after surgery might now be reversing.

Adverse outcomes related to overprescribing of opioids after surgery

Historically, research on the adverse effects of opioids in the perioperative period have focused on known short-term side-effects such as respiratory depression, itching, nausea, and constipation.[46] However, increasing attention has been paid to the relationship between postoperative opioid prescribing—particularly in the outpatient or after hospital discharge setting—and prescription opioid misuse and diversion, the development of opioid use disorder, and opioid overdose.

Panel 1: Key terms describing opioid-related outcomes

Prescription opioid misuse
Use of a prescription opioid medication in a manner or dose other than directed by a physician. Prescription opioid misuse done with the intent to feel euphoria is sometimes referred to as prescription opioid abuse.[47]

Opioid use disorder
A medical condition characterised by a problematic pattern of prescription or illicit opioid use that causes clinically significant impairment or distress.[48]

Opioid diversion
Transfer, by any means, of a legitimately prescribed opioid medication to a party other than the individual to whom it was originally prescribed.[49]

New or unintended prolonged opioid use
Receipt of opioids via prescription or diversion over an extended period of time among individuals not previously using opioids, with or without a formal diagnosis of opioid misuse or opioid use disorder; various time windows have been used in the literature for defining new or unintended prolonged opioid use.[50]

Association of postoperative opioid prescribing with opioid misuse and opioid use disorder

Panel 1 presents key terms related to adverse opioid-related behaviours; available data suggest an association between postoperative opioid prescribing practices and such behaviours. Brat and colleagues[51] evaluated the association of postoperative opioid prescribing with indicators of new-onset opioid misuse and found that the total duration of the opioid prescription after surgery was strongly associated with an increased rate of misuse, with each refill associated with an increase in the rate of misuse. Although this study tried to exclude those with a history of opioid misuse, it is important to note that the observational design prevents firm conclusions regarding a causal link between the exposure and outcome, because predisposition to addiction or misuse may also play a causal, upstream role.

Postoperative opioid prescribing and risk of opioid diversion

Opioid diversion represents an important contributor to opioid misuse. For example, in a 2015 survey of US adults, approximately 65% of those with opioid misuse in the previous year reported obtaining opioids from a source other than a physician's prescription.[9] Excess pills stored in homes have been identified as an important source of diversion to relatives or friends, or other parties through sale or theft.[52,53] Overprescribing of opioids after surgery increases the likelihood that patients will have

Panel 2*: Selected risk factors associated with prolonged opioid use after surgery

System risk factors

- Type of surgery[63,65]
- High dosage of prescriptions[70]
- Longer duration of initial prescription[70]

Patient risk factors

- Age[65] (aged 50 years or older)
- Sex[65] (male)
- Household income[63] (lower)
- Specific comorbidities[63–65,71] (diabetes; heart failure; pulmonary disease)
- Mood disorders[65,71] (depression)
- Preoperative opioid use[72]
- Early postoperative opioid use[62]
- Specific preoperative medications[63,65,66] (benzodiazepines; antidepressants; ACE inhibitors)
- Preoperative history of drug abuse[64–66]
- Preoperative tobacco use[64,66]
- Preoperative pain disorders[64,66]

*Variable definitions for prolonged opioid use—see specific references.

unused opioids after postoperative pain has resolved, with the potential to create opportunities for drug diversion. In a study[54] of patients who underwent urological surgery, 58% of the opioids dispensed immediately after surgery were consumed; 67% of patients had surplus medication from the initial prescription, and 91% of these individuals reported keeping this surplus medication at home. Similar data on excess pills have been reported after other low-risk surgery, such as dermatological surgery and hand surgery.[55,56]

Association of postoperative opioid prescribing with new prolonged opioid use

Since the development of opioid use disorder and related harms increase with greater degrees of opioid exposure and longer durations of opioid use,[57–61] understanding the association between postoperative opioid use and the initiation of prolonged opioid prescribing carries potentially important implications for public health.[50] However, such studies should be interpreted cautiously with regard to the insights they provide into such phenomena because many do not explicitly measure the incidence of opioid misuse or opioid use disorder via formal screening of enrolled participants or via presence of relevant diagnosis codes in administrative health databases. Moreover, no consensus currently exists as to what interval of prescribing should be used in defining new persistent, prolonged, or chronic opioid use. For the purposes of this Series, we will use the term prolonged opioid use as a generic term to describe any outcomes that identify extended use.

In one population-based study in Ontario assessing opioid-naive patients aged 66 years and older undergoing one of four low-risk procedures, Alam and colleagues[59] observed a marked association between the administration of opioids after surgery and prolonged opioid use as assessed at 1 year. Overall, 7·7% of previously opioid-naive patients were identified as receiving an opioid prescription at 1 year after surgery, and those patients who received postoperative opioids were 44% more likely to have a prescription at 1 year than were those who did not fill an early prescription. Subsequent work, also done in Ontario suggested potentially lower rates of new prolonged opioid use after surgery depending on the surgical population examined.[63] Both of these studies used a cross-sectional assessment of opioid filling during these periods as proxies for prolonged opioid use, but neither study specifically assessed the opioid consumption over the interval examined; the absence of a control group that accounts for prevalent patterns of opioid prescribing in the general population limits inferences from either of these studies as to the causal relationship between postoperative prescribing and new prolonged opioid use.

Efforts to characterise variations in prolonged opioid use across different types of surgical procedures have produced conflicting results, which could relate to differences across studies in the definitions used for prolonged opioid use. Brummett and colleagues[64] used prescribing claims data to compare the likelihood of receiving an opioid prescription between 90 and 180 days after surgery within a cohort of 36 177 opioid-naive adults from the USA aged 18–64 years; the percentages of patients receiving an opioid prescription at 90–180 days were qualitatively similar for patients undergoing minor or major surgical procedures, ranging from 5·9% to 6·5%. Sun and colleagues[65] observed variability across surgical procedures in the probability of new prolonged opioid use, defined as filling ten or more prescriptions or more than 120 days' supply of an opioid within a year; among 641 941 opioid-naive patients undergoing any of the 11 selected surgical procedures prolonged opioid use in the first preoperative year ranged from 0·12% for caesarean delivery to 1·41% for total knee arthroplasty.[65] The low rate of new prolonged opioid use among women undergoing caesarean sections was also observed by other authors.[66] The absence of differentiation between minor and major surgical procedures with regard to prolonged opioid use, as well as the variability between procedures observed by Sun and colleagues is consistent with observations that the size of the surgery is not a strong determinant of either acute or chronic postsurgical pain.[33, 67–69]

Factors associated with prolonged opioid use

Beyond specific surgical procedure, other patient factors identified as associated with an increased risk of prolonged opioid use included younger age, lower household income, specific comorbidities (eg, diabetes), and specific mental illness such as depression, which is then correlated

with the use of specific drugs (eg, benzodiazepines and selective serotonin reuptake inhibitors) in the preoperative period (panel 2).[63] Non-randomised evidence from prescription records in emergency department settings[73] and mixed patient populations,[74] including patients who had surgery, have suggested that larger initial opioid prescriptions and longer duration of an initial prescription could be associated with subsequent transition to prolonged opioid use.[59,70,74] However, another US study[75] of patients who had surgery found no association between the total morphine equivalents provided in the initial prescription and the likelihood of a second prescription (refill) after surgery for patients undergoing a range of major and minor procedures.

Because of the retrospective, observational design of available studies on determinants of new prolonged opioid use after surgery, the associations reported in these studies cannot be interpreted as causal in nature because of the potential for residual confounding, even after risk adjustment. For example, analyses based on health administrative data do not include data on differences in preoperative or postoperative pain symptoms between patients who did and did not fill opioid prescriptions after surgery.[62] This represents an important potential limitation to studies that have found associations between initial exposure and new prolonged use because greater experiences of pain immediately after surgery could be associated with a greater likelihood of developing chronic pain.[76] The prevalence of chronic postsurgical pain is not quantified in these studies.[68,69] Finally, the role of hyperalgesia associated with opioid use in creating a cycle of perceived need for opioids over time is also not addressed in these studies.[77]

Strategies to mitigate inappropriate opioid prescribing and related adverse effects

Individual patient interventions

Concerns regarding overprescribing have led to a range of efforts in the USA and elsewhere to reduce prescribing after surgery. In settings with high rates of opioid use for acute pain treatment, multiple studies suggest the potential to reduce the quantity of opioids dispensed without compromising effective pain control—an essential component to ensuring high-quality postoperative care. In a survey of patients who underwent caesarean delivery at six academic medical centres in the USA, Bateman and colleagues[78] observed no association between quantity of opioids dispensed and measures of patient satisfaction, the need for refills, or pain scores at 2 weeks; yet there was a direct correlation between the quantity dispensed and consumed and the rate of opioid related side-effects. Similarly, Lee and colleagues[79] found no association between hospitals' mean quantity of oral morphine equivalents dispensed after surgery and reported pain scores on standardised surveys of patient satisfaction.

Building on this work, one focus of interventions is a model of shared decision making that incorporates efforts to educate patients about appropriate expectations for pain control after surgery[20] and the risks and benefits of opioid pharmacotherapy. Prabhu and colleagues[80] developed and tested a shared decision-making tool for opioid prescribing after caesarean delivery. The tool provided information on the expected patterns of pain resolution and outpatient opioid consumption, risks and benefits of opioids and alternatives, and information about how to dispose of leftover medications. After the shared decision-making session, the patient selected the number of tablets they wanted to be prescribed, up to a limit of 40 tablets of oxycodone 5 mg. Testing this approach in 50 patients, the median number of tablets patients chose was half of the usual amount prescribed.[80] Despite this, 90% of patients reported being satisfied or very satisfied with their pain management, and only 8% of patients required refills of prescriptions.

Studies on the correlation of predischarge opioid prescribing with use after discharge also suggest the potential for alternative approaches to individualising opioid prescribing after surgery. Chen and colleagues[81] identified that 36% of patients from a surgical cohort received no opioids in the 24 h before discharge; yet 46% of this group were prescribed opioids at the time of discharge. Similarly, a study[82] of an enhanced recovery programme after surgery for patients who underwent colorectal surgery was highly effective in decreasing intraoperative opioid use; however, the frequency of opioid prescribing at the time of discharge was not greatly affected by the programme, with opioids commonly being prescribed at discharge even to patients who had low levels of opioid use over the final portion of their hospital stay, showing the potential importance of focusing on prescribing practices at discharge. Hill and colleagues[83] observed similar patterns in a sample of patients undergoing a range of surgical procedures, estimating that by using an algorithm that couples the dose dispensed at hospital discharge to opioid consumption in the previous day, the total number of opioids pills prescribed could be decreased by 40% while still meeting the home opioid treatment requirements for 85% of patients. Further prospective testing of these interventions is required to assess their potential effects on prescribing and health in practice.

Alongside efforts to tailor opioid dispensing, an additional focus of interventions has been the use of opioid-sparing or even opioid-free approaches to anesthesia and analgesia.[84] These include non-opioid systemic medications such as acetaminophen, gabapentin, or non-steroidal anti-inflammatory drugs, or regional anaesthetic techniques (eg, epidural catheters and peripheral nerve blocks).[85–87] These approaches are particularly recommended for the perioperative care of the subset of patients who might be on preoperative opioids, although data to support this approach are sparse.[88,89] Outside of the surgical context, emerging

evidence has emphasised the potential for effective treatment of even severe pain without opioids. For example, a study[90] of patients presenting to emergency departments with moderate to severe acute extremity pain found no meaningful differences in pain reduction at 2 h among patients randomly allocated to receive ibuprofen and acetaminophen versus patients receiving one of three combinations of acetaminophen plus an opioid.

To date, studies on the effect of opioid-sparing approaches on prolonged opioid use have reported mixed results. In a large cohort of patients undergoing open abdominal surgical procedures, Ladha and colleagues[91] examined the effect of perioperative epidural placement on the time to opioid discontinuation after discharge. After controlling for a range of confounders, they observed no effect of epidural placement on prolonged opioid use. Similarly, in patients undergoing either total knee or shoulder arthroplasty, Sun and colleagues[92,93] did not find an association between the use of peripheral nerve blocks and prolonged opioid use. By contrast, in a randomised controlled trial by Hah and colleagues[94] in patients undergoing orthopaedic, thoracic, and general surgeries, perioperative gabapentin was associated with a modest increase in the rate of opioid cessation after surgery (hazard ratio 1·24, 95% CI 1·00–1·54). One potential explanation for the modest or negligible effect observed in these studies could be that discharge opioid prescribing behaviours for inpatients who undergo surgery inadequately incorporate information on pain or opioid requirements over the course of the hospital stay.[81] Future efforts to maximise the potential for multimodal analgesia approaches to affect postoperative opioid use might require pairing them with tailored approaches to opioid prescribing for individual patients at the time of discharge.[83]

Opioid overdose following hospital discharge after surgery is relatively rare, but the risk is substantially elevated above baseline levels.[95] The increase is greatest among patients on high doses of opioids preoperatively (≥50 morphine equivalents daily).[96] Opioid overdoses can be reversed through the administration of naloxone, which is an opioid antagonist. Many states in the USA passed laws in recent years to increase the accessibility of naloxone, including allowing dispensing of the medication without prescriptions,[97] and programmes to distribute naloxone appear to decrease rates of overdose in communities.[98] However, the utility of dispensing naloxone to postoperative patients has not been well defined and is an important topic for future research.

Hospital or health system interventions

Several studies show the steps taken at the individual health system level in the USA to directly address opioid overprescribing. For example, Hill and colleagues[83] formulated local guidelines for postoperative opioid prescribing for five common outpatient procedures (partial mastectomy, partial mastectomy with sentinel lymph node biopsy, laparoscopic cholecystectomy, laparoscopic inguinal hernia repair, and open inguinal hernia repair) and encouraged the use of acetaminophen and non-steroidal anti-inflammatory medications instead of opioids.[99] This intervention decreased the quantity of opioids prescribed by surgeons by 53%, with repeat opioid prescriptions required by only 0·4% of patients.

Other approaches leverage established principles of behavioural economics to use default prescribing options to nudge physicians towards more appropriate prescribing targets. Several studies in non-surgical settings have evaluated the use of setting default quantities for commonly prescribed opioids as a way of encouraging judicious prescribing.[100,101] In the context of perioperative prescribing, Chiu and colleagues[102] found marked decreases in both the number of opioid pills prescribed and total morphine equivalents prescribed after ten common surgical procedures in one large urban health system when the default number of pills on all electronic opioid prescriptions was lowered from 30 to 12. Notably, this change occurred without either a corresponding increase in the rate of opioid refills among patients who underwent surgery or a decrease in prescriptions for quantities smaller than the default level.[102]

Other interventions have targeted the disposal of leftover opioids.[103,104] Hasak and colleagues[104] found that providing patients who underwent surgery with a brochure describing how to properly dispose of opioids and locate take-back locations resulted in an increase in the frequency with which patients disposed of leftover medication. Because of the importance of leftover medication as a source of opioids that are misused, additional studies of behavioural interventions to encourage disposal are indicated.

Because of the known relationships between depression, anxiety, and catastrophising and chronic postsurgical pain and persistent opioid use,[65,71,105] there can be opportunities to provide psychiatric support that could affect postoperative opioid use.[106] One model of this is a multidisciplinary programme that incorporates psychological support as part of a broader platform of interventions to prevent chronic postsurgical pain.[107,108] Preliminary data from this approach show reductions in opioid use and pain interference and reductions in depressed mood.[109] Because of the prevalence of mood disorders in the general population,[110] such interventions may be a key to improved outcomes; they might also be helpful for support of patients with preoperative opioid use, who can present specific challenges with regard to postoperative care.[108]

Improving practice guidelines

A key historical challenge to improving opioid prescribing for patients who undergo surgery on a large scale has been an absence of consensus regarding appropriate prescribing targets for individual patients or populations.

Drawing primarily on evidence from the emergency medicine literature, the 2016 Centers for Disease Control and Prevention Guideline for the Prescribing of Opioids[111] stated that for most acute pain conditions, 3 days of opioid treatment or less should be adequate, and more than 7 days of treatment is rarely needed (although postsurgical prescribing was noted to be beyond the scope of these guidelines).

In the USA, multiple groups have since worked to develop prescribing recommendations that are procedure specific using data on medication refill claims and patient surveys. Using pharmacy claims for approximately 200 000 US patients, Scully and colleagues[112] recommended optimal prescribing durations for postoperative opioids of 4 to 9 days for general surgery procedures, 4–13 days for women's health procedures, and 6–15 days for musculoskeletal procedures on the basis of the observed median prescription length and the nadir of the modelled probability of obtaining a refill after the initial prescription. In a separate effort, investigators from the University of Michigan's Opioid Prescribing Engagement Network (OPEN) published recommended prescribing regimens for postoperative opioids; OPEN recommendations define an upper limit for postoperative opioid prescribing defined as the amount required to meet or exceed self-reported postoperative opioid use in 75% of patients based on surveys of postoperative pain and opioid consumption (table).[113,114] The creation of protocolised, procedure-specific upper limits for opioid prescriptions could help to depersonalise the processes around postoperative pain management,[115] preserving the patient–doctor therapeutic alliance when patients request inappropriately large quantities.

	Maximum recommended tablet count (oxycodone 5 mg or hydromorphone 2 mg)
Laparoscopic cholecystectomy	10
Laparoscopic appendicectomy	10
Inguinal or femoral hernia repair (open or laparoscopic)	10
Open incisional hernia repair	10
Laparoscopic colectomy	15
Open colectomy	15
Ileostomy or colostomy creation, re-siting, or closure	15
Open small bowel resection or enterolysis	20
Thyroidectomy	5
Vaginal hysterectomy	15
Laparoscopic or robotic hysterectomy	15
Abdominal hysterectomy	15
Breast biopsy or lumpectomy alone	5
Lumpectomy with sentinel lymph node biopsy	5
Sentinel lymph node biopsy alone	5
Simple mastectomy with and without sentinel lymph node biopsy	20
Modified radical mastectomy or axillary lymph node dissection	30
Wide local excision with and without sentinel lymph node biopsy	20

Table: **Michigan Opioid Prescribing Engagement Network postoperative opioid prescribing recommendations for surgery among patients without previous opioid use (selected)[108]**

Policy interventions

Limiting the duration of initial opioid prescriptions for acute pain indications has been the focus of several policy initiatives. After the 2016 CDC guidelines, multiple US states implemented legislation limiting first-time opioid prescriptions to a 7 day supply.[116–118] A substantial challenge to this approach, which might compromise the effect of these policies, is that there is no clear definition of what constitutes a day's supply after most surgical procedures. Therefore, a 7 day supply could represent a very large amount of medication if the physician assumes that the patient takes a dose at regular intervals for all 7 days (eg, two tablets every 4 h for 7 days would result in a prescription for 84 pills).[83] Imposing prescription limits also has the potential to result in an inadequate supply for some patients, and systems need to be in place to insure timely access to additional opioids when needed. One possible support solution is the implementation of electronic prescribing of opioids that allows physicians to write for additional opioids remotely.[119]

Other policy initiatives aimed at reducing opioid-related harms have also gained traction. Prescription Drug Monitoring Programs (PDMPs) are databases that contain patient-level information on filled prescriptions for controlled substances. These are now available in nearly all US states, although requirements vary regarding their use.[116] They are useful for detecting patients who are seeking opioid prescriptions from multiple different physicians or who are co-prescribed medications that increase the risks associated with opioids, such as benzodiazepines. Some studies have reported an association between the implementation of PDMPs and a reduction in overall opioid prescribing, but data are mixed.[120–122] In patients who underwent surgery, the use of PDMPs might have particular utility in the early detection of patients transitioning to unintended prolonged use. Other policy initiatives have targeted reducing the supply of leftover medication in communities. These initiatives include introducing secure medication disposal boxes (drop-boxes) in medical facilities, law enforcement offices, or pharmacies,[123,124] and drug take-back events.[125] Aligned with such initiatives are public outreach efforts, such as the Rx Awareness campaign[126] by the US Centers for Disease Control and Prevention and the The Truth About Opioids campaign,[127] by the US Truth Initiative—both rely on a combination of digital and traditional media approaches to raise awareness about the risks associated with opioid analgesics and discourage inappropriate use.

Health-care payers have also begun to initiate programmes to address overprescribing of opioids.[128] The Centers for Medicaid and Medicare Service, which administers public insurance programmes in the USA, implemented numerous programmes that focused on

this issue, including developing national quality improvement networks and sending letters to physicians who prescribe opioids at higher levels than do their peers. Their recently released roadmap to address the opioid epidemic highlights plans for further work to identify and curb overprescribing of opioids and to encourage the use of effective non-opioid pain treatments.[129]

There is also growing recognition of the need to improve medical student education on opioid prescribing. One study[130] has noted a relationship between medical school rank of schools where physicians received their degrees and opioid prescribing practices. The study showed that physicians trained at the lowest ranked US medical schools prescribed nearly three times as many opioids per year as did physicians trained at the top school, raising the possibility of education-based interventions to improve opioid prescribing. However, it is important to note that the finding was most pronounced for primary care physicians and less so for surgical specialists. Government agencies have recognised the importance of improving medical curricula on prescription opioid use. For example, in Massachusetts the Department of Public Health co-led a working group with representatives from the state's medical schools to define core competencies related to prescription drug misuse.[131]

Conclusion

Global increases in prescription opioid use over the past decade, along with an epidemic of opioid misuse and related harm, have led to a recognition of opioid overprescribing in the postoperative setting as a pronounced problem in some countries, with serious potential adverse consequences for public health. In settings where opioid overprescribing after surgery appears to be common, such as the USA and Canada, efforts are ongoing to identify and implement effective interventions at the patient level, health system level, and policy level to discourage excess opioid prescribing and prevent related misuse and diversion. For countries in which access to opioids is limited but expanding, the experiences described in this Series show the importance of establishing and implementing evidence-based standards to encourage responsible opioid prescribing while also promoting effective pain management for patients after surgery.

Contributors

All authors contributed to the drafting and revision of this paper.

Declaration of interests

BTB is an investigator on grants to Brigham and Women's Hospital from the US Food and Drug Administration, Baxalta, GSK, Lilly, Pacira, and Pfizer for unrelated work; and a paid consultant to Aetion, Inc, and the Alosa Foundation. MDN and HW declare no competing interests.

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Postoperative pain management and opioids 3

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

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This is the third in a Series of three papers about postoperative pain management and opioids

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Opioids are a mainstay of acute pain management but can have many adverse effects, contributing to problematic long-term use. Opioid tolerance (increased dose needed for analgesia) and opioid-induced hyperalgesia (paradoxical increase in pain with opioid administration) can contribute to both 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 μ opioid receptor signalling pathways that offer opportunities for novel analgesic alternatives. The intracellular scaffold protein β-arrestin-2 is implicated in tolerance, hyperalgesia, and other opioid side-effects. Development of agonists biased against recruitment of β-arrestin-2 could provide analgesic efficacy with fewer side-effects. Alternative approaches include inhibition of peripheral μ opioid receptors and blockade of downstream signalling mechanisms, such as the non-receptor tyrosine kinase Src or N-methyl-D-aspartate receptors. Furthermore, it is prudent to use multimodal analgesic regimens to reduce reliance on opioids during the perioperative period. In the third paper in this Series we focus on clinical and mechanism-based understanding of tolerance and opioid-induced hyperalgesia, and discuss current and future strategies for pain management.

The evolution of opioid analgesia

Humans have used opioid alkaloids in resin harvested from the opium poppy (*Papaver somniferum*) for thousands of years to suppress pain and for hedonic effects. Merck began extracting morphine in the 1820s, and the first synthetic opioid analgesics appeared 100 years later. Despite having disparate structures, both natural and synthetic opioids bind to μ opioid receptors. The μ 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, gut, and chemotrigger zone also contain μ receptors; activation of these receptors results in respiratory depression, constipation, and nausea.[2] Opioid analgesics have additional detrimental effects, including tolerance (increasing doses are required to maintain analgesia), dependence (physical and psychological), hyperalgesia (a paradoxical increased sensitivity to pain) (figure 1), and addiction (inability to control continued use, despite harm or negative consequences).[1,4] 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.[5] 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.[6]

Because of the adverse effects associated with opioid use, it is logical to look for alternative approaches to treat severe pain. Although there are other targets within the pain pathway for the future development of drugs, including the δ and κ opioid receptors,[7] μ receptors remain the most important analgesic targets. Despite considerable investment, no new drugs have usurped opioids as the pre-eminent analgesics for treating severe pain, particularly in the acute setting. The endurance of opioid analgesics is perhaps not surprising considering the strategic location of μ receptors and the role of the endogenous opioid system in regulating pain sensitivity.[1]

Opioid analgesia in the 21st century

Chronic pain, including persistent postsurgical pain,[8] affects approximately 20–50% of the world's population.[9] As one of the leading causes of disability globally, chronic pain is a major public health problem.[10] 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 could be a more useful approach for patients and health-care professionals. However, many patients with chronic pain are prescribed an opioid. Opioids are now one of the most commonly prescribed medications in the USA with similar, although less marked, trends in other countries including the UK.[11,12] Although pain reduction by pharmacological means can be advantageous, there is little evidence for the long-term benefit of opioids.[13]

There have been unintended consequences of a liberal prescribing policy, particularly in the USA where long-term harms from prescription opioids have become much more apparent, including addiction, misuse, and increased mortality.[14,15] Although opioid use in chronic pain can appear to be distinct from the perioperative setting, prolonged opioid exposure creates additional challenges when trying to manage acute pain.[16–18]

Furthermore, we need to consider what role surgery and postoperative opioid prescribing have in initiating long-term opioid use (panel 1),[19] as covered in detail in this series.[20]

The use of synthetic (eg, fentanyl and remifentanil) or natural (eg, 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,[21] and postoperative opioid analgesia that is patient controlled improves comfort and patient satisfaction.[22] However, the use of perioperative opioids can predispose patients 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 every week of repeat prescription after discharge.[17,23] 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.[16,24] However, linkage of perioperative anaesthesia and analgesia to long-term outcomes such as opioid prescribing, using routinely collected heath-care data, is scarce.

This paper will focus on the use of opioids in the perioperative setting, particularly on clinical and mechanism-based understanding of tolerance and opioid-induced hyperalgesia (OIH). By improving understanding of the underlying mechanisms, it might be possible to develop strategies to identify and better manage post-operative pain and pain after injury 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, which is evidence that this endogenous pain control mechanism has evolved over hundreds of millions of years.[25] Three genes encode endogenous opioid peptides,[26] most of which have some activity at each of the three main opioid receptor subtypes (μ, κ , and δ) with some subtype preferences.

Opioid analgesics activate μ 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 βγ subunits (figure 2).[27] The result is decreased neuronal excitability, with reduced excitatory neurotransmitter release in pain pathways.[28,29] By contrast, activation of μ receptors in the brain's reward circuitry inhibits inhibitory neurotransmission in the ventral tegmental area, reducing the frequency of γ-aminobutyric acid (GABA) inhibitory postsynaptic events, thereby disinhibiting dopaminergic neurones and increasing dopamine release into the striatum and prefrontal cortex (table 1).[31,32] Enhanced dopamine release causes D2 receptor-dependent reinforcement.[33] However,

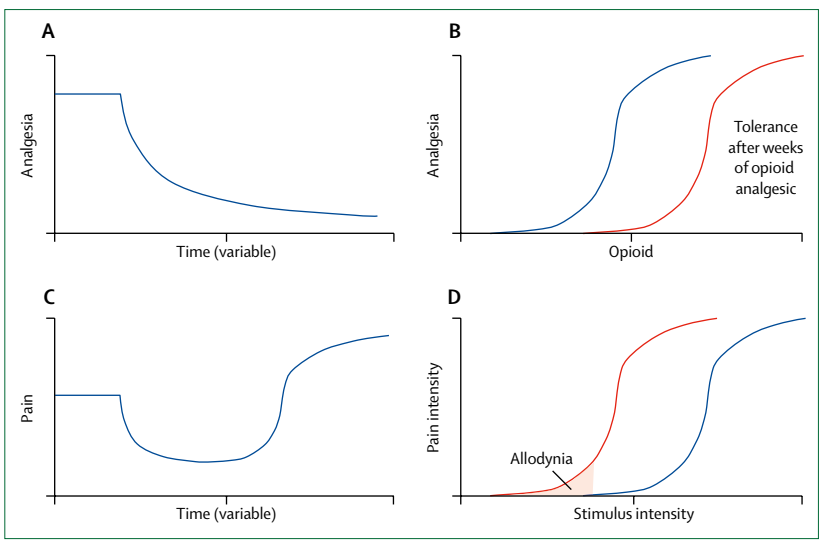

***Figure 1*: Changes in opioid analgesia and pain during tolerance and hyperalgesia**
(A) Tolerance to opioid analgesia develops after ongoing exposure to the drug. The same dose of drug administered over time produces less analgesic effect. The rate of onset and extent of tolerance development is variable depending on the individual drug and patient characteristics. (B) Opioid analgesic tolerance produces a rightward shift in the dose–response relationship. (C) Opioid-induced hyperalgesia describes a paradoxical increase in pain sensitivity during ongoing exposure to opioid drugs. Although the timeline in the graph is not specified, and will vary between different opioids, in the case of remifentanil (0·1 μg/kg per min),[1] infusion for 30 min is sufficient to cause opioid-induced hyperalgesia.[3] (D) Allodynia can occur after exposure to an opioid (ie,pain in response to stimuli that were of intensities [shaded red] below threshold before drug administration).

***Panel 1*: Clinical issues that arise from opioid use in the acute setting and the factors that need to be considered**

Acute presentation of patient on regular opioid prescription (ie, not opioid naive)
- Pain control difficult
- Likely to have pre-existing tolerance, and therefore higher doses might be needed to achieve analgesia
- Might have opioid-induced hyperalgesia, and therefore a reduced opioid dose and alternative strategies might be needed

Opioid-naive patient treated with short acting perioperative opioid as part of the anaesthetic regimen
- Acute tolerance
- Development of opioid-induced hyperalgesia
- If rapid cessation, acute opioid withdrawal might occur

Opioids prescribed to allow early discharge
- Increased prescribing of opioids for longer postoperative period leading to sustained use
- Dependence (physical and psychological)
- Increased potential for drug diversion if opioids not used by patient for whom prescribed

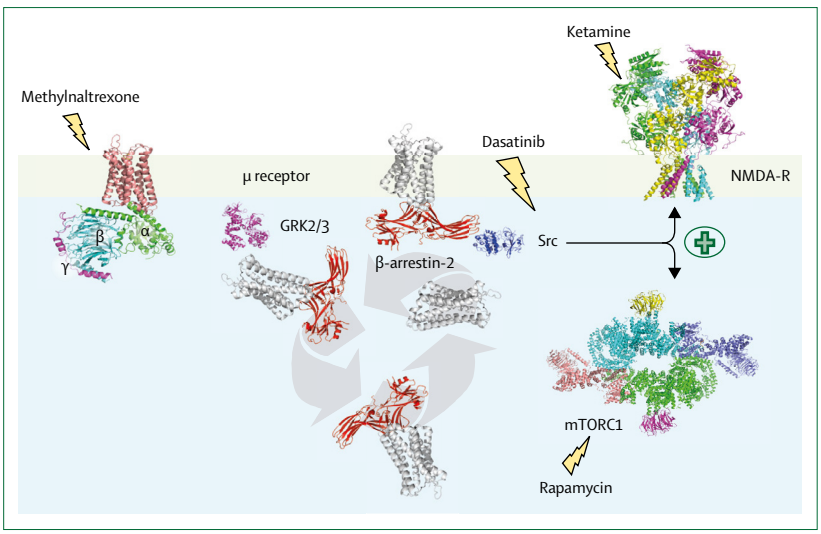

***Figure 2*: Available drugs that reduce opioid tolerance and/or hyperalgesia in preclinical studies through proteins in the μ receptor signalling pathway**

The peripherally restricted antagonist methylnaltrexone reduces morphine tolerance and hyperalgesia by inhibiting μ receptors on nociceptive neurones. The leukemia drug dasatinib attenuates and reverses morphine tolerance via inhibition of the tyrosine kinase Src. The multipurpose drug rapamycin inhibits the mammalian target of rapamycin (mTOR), reducing morphine tolerance and hyperalgesia. The dissociative anaesthetic ketamine reduces opioid-induced hyperalgesia through inhibition of N-methyl-D-Aspartate (NMDA) receptors. G protein $G\alpha_{i/o}$ and βγ subunits, G protein receptor kinase 2/3 (GRK2/3), NMDA receptor, and mTORC1 β-arrestin-2 are all represented as ribbon diagrams. Protein Data Bank source files: 6DDE, 1YM7, 3P2D, 5FX1, and 5FLC, respectively.

	Possible mechanisms
Acute administration	
Analgesia	Decreased excitatory transmission in pain pathway
Nausea	Chemoreceptor trigger zones
Respiratory depression	Brain stem nuclei
Constipation	Inhibition of myenteric neurons with decreased acetylcholine
Reward	Decreased inhibitory transmission in the ventral tegmental area and increased dopamine
Rapid tolerance and opioid-induced hyperalgesia	See panel 2
Chronic administration	
Tolerance, dependence, and opioid-induced hyperalgesia	See panel 2
Constipation	Inhibition of myenteric neurons with decreased acetylcholine
End of treatment	
Withdrawal	Increased glutamate; increased nor adrenaline; increased corticotrophin-releasing factor; decreased dopamine; and decreased 5-hydroxytryptamine

Some of the key processes that contribute to analgesia and the detrimental effects of opioids.[1,2,30]

***Table 1*: Opioid effects with acute and chronic exposure**

morphine also has reinforcing effects in mice engineered to not produce dopamine, an observation that implicates alternative mechanisms.[34]

Consequences of prolonged opioid exposure

The μ receptor has several serine, tyrosine, and threonine sites of phosphorylation, mostly in its C-terminus, which interfaces with the G protein.[1,27]

Opioid receptor activation can lead to phosphorylation by GPCR kinases (GRKs), mitogen-activated protein kinase (MAPK), c-jun-N-terminal kinase (JNK), protein kinase A (PKA), protein kinase C (PKC), Src kinase, and Ca^{2+}/calmodulin dependent kinase II (CAMKII). Furthermore, inhibition of several of these kinases reduces tolerance and hyperalgesia (panel 2).[1,30,35–38] μ receptor phosphorylation by GRKs (of which there are seven forms) leads to β-arrestin-2 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 μ receptor expression at the cell membrane can contribute to tolerance. Heterozygous mice in which μ receptor expression is 50% of wild-type mice exhibit more rapid and profound morphine tolerance.[38] In humans the endogenous opioid system contributes to pain sensitivity,[39] and a loss of μ receptors caused by prolonged exposure to opioid analgesics might also heighten sensitivity to pain leading to OIH. Tolerance caused by endogenous opioids has been implicated in the hypersensitivity of patients with fibromyalgia.[40] However, morphine, which causes tolerance and OIH, has little effect on μ receptor endocytosis even with prolonged exposure.[41] By contrast, the selective peptide agonist DAMGO produces marked receptor endocytosis with little tolerance and therefore the relationship between endocytosis and tolerance is complex. Instead, endocytosis might be required to reverse desensitisation, a rapid form of tolerance observed at the cellular level.[42]

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.[43] Furthermore, the extents and rates of the development of tolerance differ for different opioid effects. Differences in tolerance to respiratory depression and analgesia can be explained by their differing molecular mechanisms.[44] 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 can be unpredictable, with a narrow therapeutic window between desired effects (usually analgesia) and undesirable respiratory or gastrointestinal effects.[45] Acute tolerance can be hard to distinguish from other opioid related effects, such as OIH (table 2). Key features to assess include the response to additional opioid: with tolerance, an increased opioid dose should be effective, although very high doses can be required (figure 1); similarly, a reduction in opioid dose would be expected to produce

Panel 2: **Cellular mechanisms implicated in tolerance and hyperalgesia**

μ opioid signalling
- Increased cyclic adenosine monophosphate and protein kinase A
- Protein kinase C
- C-Jun N-terminal kinase
- β-arrestin-2
- Src kinase

Transcriptional mechanisms
- cAMP response element-binding protein
- Mammalian target of rapamycin complex 1

Pronociceptive ion channels
- N-methyl-D-aspartate receptors
- Transient receptor potential vanilloid channels

Microglia
- Toll-like receptor 4
- P2X4 and P2X7 purinergic receptors
- Src kinase
- Brain-derived neurotrophic factor

increased pain (but not hyperalgesia). Additionally, in patients with tolerance but without OIH there should be no signs of reduced pain thresholds and hyperalgesia, apart from around the immediate injury site.[55]

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 with patients taking non-opioid analgesics. This can reflect OIH (figure 1), or pre-existing reduction in endogenous pain inhibition, which increases the likelihood of long-term opioid use.[56] Non-opioid perioperative analgesia might 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.[52,57,58] A 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 did those on non-opioid analgesics.[59] The risk of developing chronic postsurgical pain, in addition to OIH and tolerance, must also be considered, with a role for transitional pain clinics to ensure correct opioid management.[8]

In some chronic pain states there is evidence that dysfunction in the endogenous opioid systems can lead to development of hyperalgesia, with a potential site for this within the brainstem.[40,59] 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 risk factors, or a consequence of opioid therapy, care must be taken in managing these patients to avoid further opioid-related complications such as OIH.

	Suggested management approach
Opioid-induced hyperalgesia[46-48]	
Hyperalgesia in response to opioid administration or increased opioid dose	Reduce opioid dose
Might not be at site of pre-existing injury	Use adjuvants targeting mechanisms (eg, reduce NMDA receptor activity via drugs such as ketamine)
Descriptors used might be neuropathic in nature	Mixed evidence for opioid rotation (mainly long-term use)
Tolerance[43]	
Increased opioid dose required to achieve the same level of analgesia	Increase opioid dose
Despite no change in underlying cause of pain	Rotate opioid
Can occur in both acute and chronic settings	Use adjuvants targeting mechanisms
Acute neuropathic pain[49-51]	
Signs and symptoms compatible with neuropathic pain	Consider use of screening tools for non-specialists
Known injury or damage to the peripheral or central nervous system	Use specific anti-neuropathic medication such as gabapentinoids and ketamine (although evidence is inconclusive for acute pain)
Defined area affected	Option to use targeted topical therapies (eg, lidocaine 5% patch; capsaicin 8% patch)
Acute opioid withdrawal[52-54]	
An increase in local and widespread pain	Assess using COWS scale; reduce rate or size of opioid reduction
Often associated with anxiety, distress, and gastrointestinal upset; autonomic dysfunction	Symptomatic relief of withdrawal symptoms

COWS=clinical opioid withdrawal scale.[53] NMDA=N-methyl-D-aspartate receptors.

Table 2: **Differential diagnosis of inadequate postoperative pain control**

Identifying hyperalgesia in patients

Although there is extensive preclinical evidence of OIH with changes in the underlying neurobiology leading to a pronociceptive state (table 1), as well as evidence from human volunteer studies, there is still debate about the clinical manifestations of OIH. This could be partly because some studies do not 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 consider other potential causes such as inadequate analgesia, changing underlying disease pathology, or 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 hyperalgesia.[60] There might be some merit in the use of techniques such as quantitative sensory testing (QST) to assess patient responses to defined physical stimuli (thermal and mechanical), with the aim to achieve a more consistent approach to diagnosing OIH.[56] Even with QST the demonstration of hyperalgesia around the surgical site is not necessarily diagnostic of OIH because the tissue response to surgical trauma,

	Postulated mechanisms of analgesia	Comments
Simple analgesics		
Paracetamol	Possibly central inhibition of COX-mediated prostaglandin production	High-quality evidence for analgesic benefit of intravenous paracetamol and scarce opioid-sparing effects[22,74]
NSAIDs	Inhibition of COX enzymes to reduce inflammatory cytokines and chemokines	Potential issues with renal dysfunction and GI irritation[75]
Anti-neuropathic drugs and non-standard analgesics		
Gabapentin; pregabalin	Inhibition of presynaptic Ca^{2+} channels	Unclear as to optimum dose, timing, and duration[76]
Ketamine; magnesium	NMDAR inhibition	Unlikely to be sufficient in isolation[77,78]
Dexmedetomidine; clonidine	α2 adrenergic agonist	Sedative; postural hypotension[72]
Steroids	Reduce inflammatory response to surgery	Consider effect on immune function[79]
Intravenous lidocaine	Na^+ channel blockade	Low to moderate quality evidence of reduced pain, but variable reports of effects on opioid use[80]
Invasive techniques		
Nerve blocks with local anaesthetic	Blockade of action potentials through Na^+ channel blockade	Extent depends on type of local anaesthetic used, dose, volume, route, etc; single shot, catheter-based, or infusion-based techniques or PCEA[81]

Ca^{2+}=calcium. COX=cyclooxygenase. GI=gastrointestinal. Na^+=sodium. NMDAR=N-methyl-D-aspartate receptor. NSAIDs=non-steroidal anti-inflammatory drugs. PCEA=patient-controlled epidural analgesia.

Table 3: **Some suggested analgesic approaches for multimodal analgesia to reduce opioid use**

For the **PAIN OUT database** see http://pain-out.med.uni-jena.de/

with release of inflammatory mediators, can cause peripheral and central sensitisation and can be manifested as hyperalgesia. If there is more widespread hyperalgesia, then there is an increased likelihood of OIH.[61] 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.[62] The absence 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 can occur in the perioperative setting (table 2). This uncertainty is compounded by the observation that neuropathic pain often responds poorly to opioids.[63]

Clinical evidence for OIH

Identification and management of OIH is important because if untreated it can increase the risk of developing persistent postsurgical pain.[8] As outlined in table 2, care is needed to ensure that OIH is recognised and appropriately treated. However, there is continued debate as to whether OIH is a significant clinical entity.[46]

Outside the acute surgical setting, a systematic review[64] identified eight studies with evidence of OIH, but the approach to diagnosis was inconsistent and with little assessment of effect. Small studies,[65–67] using QST in a range of chronic pain conditions, show that opioid use does contribute to hyperalgesia, although this can be enhanced by other factors such as low mood. Sex differences can also occur: males who were prescribed opioid showed increased hyperalgesia with fentanyl when compared with females, and both showed reduced pressure pain thresholds when compared with healthy controls.[65–67] Increased thermal sensitivity has also been shown in patients on long-term opioids, even after adjusting for a variety of other factors.[68] This action can be a consequence of recruitment and sequestration of β-arrestin-2 after μ receptor activation, which has been shown in mice to sensitise transient receptor potential vanilloid (TRPV1) channels to thermal activation.[69]

A comprehensive systematic review[70] of OIH after surgery identified 27 studies with approximately 1500 patients. Higher doses of intraoperative opioid (mainly remifentanil) were associated with an increase in postoperative pain scores, and a higher 24 h morphine consumption. A subsequent systematic review of acute OIH and tolerance showed similar findings.[71] A large study using the PAIN OUT database found an association between worse pain-related outcomes and intraoperative use of remifentanil.[72] Other studies[73] have strengthened this finding, with younger patients seeming to be at increased risk. The cause of the apparent increased risk of OIH with remifentanil compared with other opioids is unclear, but might be related to the fast onset and 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 table 3 and figure 3.[82] Anaesthetic technique should be considered: intravenous anaesthesia with propofol can have a lower risk of OIH when compared with anaesthesia with a volatile drug. Addition of nitrous oxide can reduce the incidence of hyperalgesia.[60,83–86] If intravenous opioid infusion is considered as part of the anaesthetic regimen, then avoiding high infusion rates of remifentanil can reduce risk of OIH. Dose rates of more than 0·2 μg/kg per min can increase the risk of OIH, and for doses of more than 0·25 μg/kg per min acute tolerance can be problematic.[7] Consideration of a gradual tapering of remifentanil at the end of surgery can also reduce OIH, possibly by reducing withdrawal-induced long-term potentiation at the first central synapse in the spinal cord.[87–89] Other suggested strategies to reduce this problem include limiting the dose of remifentanil, or specifically targeting putative mechanisms using novel approaches.[90]

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

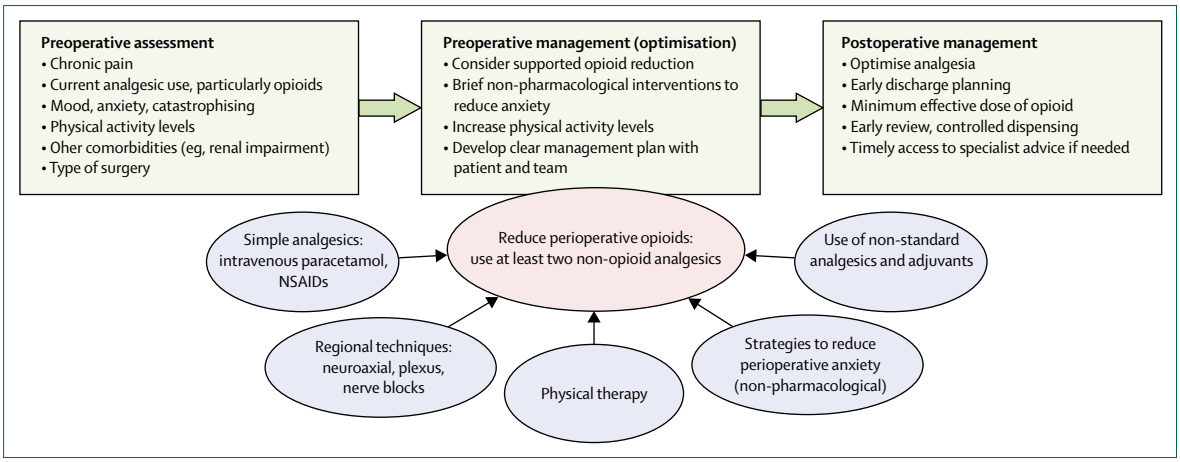

Figure 3: **Strategies to reduce perioperative opioid use**
NSAIDs=non-steroidal anti-inflammatory drugs.

pain.[8] If OIH is suspected in the immediate postoperative period it is important to address it as soon as possible. Untreated OIH makes perioperative management more difficult, with potential delay in hospital discharge.

Early assessment and diagnosis

Early assessment and diagnosis is important to effectively direct treatment (table 2). Although there is substantial overlap in the approach to tolerance and OIH, one of the key differences is that OIH can require opioid dose reduction. Therefore a reasonable first step is to assess the response to an increased opioid dose: if analgesia improves, then tolerance is more likely; but if analgesia worsens, then OIH should be suspected, and other features sought.

Use of multimodal analgesia with low or no opioid component

Some strategies have not been extensively explored with clinical studies, regarding the effect on OIH and tolerance, but do include the use of drugs outlined in table 3. These include simple analgesics such as paracetamol, non-steroidal anti-inflammatory drugs, dexmedetomidine, N-methyl-D-aspartate (NMDA) receptor antagonists (eg, ketamine), and opioid dose reduction.[49,90–92] Opioid free multimodal analgesia might be a laudable aim, but the number of patients presenting for surgery who are not opioid naive will pose a challenge. A small randomised controlled trial[93] has shown that it is possible to substantially reduce opioid consumption in such patients by using intravenous ketamine. Furthermore a Cochrane review[50] found that ketamine can reduce the risk of persistent postsurgical pain, although most of the studies were small, with possible overestimation of treatment effect. Use of more than one type of non-opioid analgesic can have most effect on opioid consumption, although there are few studies assessing combination analgesia. Use of at least two non-opioid approaches can reduce adverse effects, such as respiratory depression, gastrointestinal dysfunction, as well as reducing opioid requirements.[94,95]

Consideration of non-pharmacological strategies

Although not the focus of this Series paper, there is some evidence that the use of psychosocial techniques such as relaxation, behavioural instruction, and patient education can be beneficial in reducing postoperative pain.[96,97] The development of Enhanced Recovery After Surgery (ERAS) protocols using a multimodal approach to minimise effect of the surgical episode does incorporate optimising analgesia, but also uses early mobilisation and other techniques that can indirectly improve pain outcomes.[98]

Future approaches to managing OIH and tolerance

There are several overlapping pathways implicated in opioid induced tolerance and hyperalgesia (panel 2), many of which have been extensively reviewed.[1,30,35,36] These pathways have been implicated in enhanced pronociceptive systems (eg, TRPV1, NMDA receptors, and microglia) and diminished antinociceptive systems (eg, β-arrestin-2). Any of these pathways could provide targets for adjunct drugs that improve opioid analgesia, or their recruitment might be avoidable by agonists biased against their activation. We will focus on emerging targets affecting the endogenous opioid system, which could 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 β-adrenergic and opioid receptors (arrestin-2 and 3); commonly referred to as β-arrestin-1 and 2.[99] Receptor phosphorylation via GRK enables

recruitment of β-arrestin-2, an event that precedes endocytosis and blocks G protein interactions (figure 2).[1] Mice deficient in β-arrestin-2 exhibit hypoalgesia and a striking resistance to morphine tolerance, respiratory depression, and constipation.[38,100–103] Intrathecal β-arrestin-2 reduction also attenuates morphine tolerance in rats, indicating that this effect is not a consequence of compensatory mechanisms in arrestin-deficient mice.[104] This approach also reduced withdrawal symptoms in rats chronically administered morphine. This finding suggests that morphine analgesic tolerance and dependence involves β-arrestin-2. Additionally, β-arrestin-2 facilitates the development of pain sensitivity in mice by facilitating TRPV1 activation.[69]

Biased agonism

There is increasing evidence that some so-called biased GPCR agonists preferentially activate either G protein-mediated signalling or recruitment of β-arrestins.[105,106]

The role of β-arrestin-2 in the side-effects and other complications of opioids in mice led to a search for biased μ receptor agonists. The biased agonist herkinorin was found to activate G proteins with negligible recruitment of β-arrestin-2. It is analgesic with markedly decreased tolerance compared with morphine.[106] Herkinorin also exhibits less constipation and respiratory depression. Two more biased agonists, TRV130 and PZM21,[107] also appear to cause less respiratory depression and constipation than morphine; however, respiratory effects and tolerance were observed for PZM21[108] in a more recent study. TRV130 causes less tolerance than morphine does when administered repeatedly to rodents and was analgesic when administered intravenously to treat acute pain in phase 2 clinical studies.[107] 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 β-arrestin-2 is to inhibit signalling components to minimise the side-effects, tolerance, and OIH of available opioids (figure 2). However, β-arrestin-2 provides a scaffolding role and is not a signalling molecule in its own right and is unlikely to be a good pharmacological target. Instead, molecules upstream or downstream of β-arrestin-2 recruitment might prove more suitable targets.

The use of naloxone, to antagonise the μ receptor, provides prolonged oxycodone analgesia and reduces constipation, effects that appear to be mediated through inhibition of peripheral μ receptors.[109,110] There might be value in exploring the use of naloxone or methylnaltrexone, a peripherally restricted μ receptor antagonist, in combination with opioid agonists to reduce tolerance and hyperalgesia (figure 1). Methylnaltrexone inhibits morphine tolerance and OIH in mice by antagonising μ receptors specifically on TRPV1 expressing primary afferent nociceptive neurones.[110] 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 μ receptors might compromise opioid analgesia.[110] An alternative is to inhibit downstream targets such as c-Src, which is 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.[111] SFKs can be activated by GPCRs via Gα and Gβγ subunits,[112] and are involved in activation of intracellular signalling processes through formation of complexes with β-arrestin-2 (figure 1). Src participates in opioid receptor signaling, phosphorylation, endocytosis, tolerance, and withdrawal.[37,38,113,114]

The Src inhibitor dasatinib used clinically to treat leukaemia[115] not only attenuates tolerance in mice, but also rapidly restores analgesia diminished during the preceding days when administered before morphine.[38] Unlike deletion of β-arrestin-2, which enhances morphine reinforcement in mice, Src inhibitors appear to have no such effect. However, similar to the reduced expression of β-arrestin-2, Src inhibition diminishes opioid withdrawal in rats.[37] Additional work is needed to establish whether Src participates in other opioid side-effects such as constipation and respiratory depression. Src has also been implicated in the role of microglia in morphine analgesic tolerance (panel 2).[116]

Although Src inhibitors are not antinociceptive in acute pain,[38] they reduce hyperalgesia in rodent models of OIH, neuropathic, inflammatory, and bone cancer pain.[117–119] Hyperalgesia is associated with Src-mediated phosphorylation and up-regulation of NMDA receptors, which leads to enhanced excitatory transmission in spinal neurones.[120] Several parallels can be drawn between hyperalgesia and morphine tolerance (panel 2), including a common requirement for Src and NMDA receptor activity (figure 2).[121] 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).[122] 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?

Although opioids are strong analgesics, there are risks associated with their use in the acute setting.

Postoperative pain management of patients who are on chronic opioids is complicated by opioid tolerance, increased risk of acute withdrawal, and OIH. An acute surgical episode can lead to prolonged opioid use, with increased risk of tolerance, and OIH. There can also be prolonged postoperative prescribing for other reasons.

The approach to these challenges might be similar, aiming for optimal perioperative analgesia by using techniques and drugs to minimise opioid use (figure 3). The optimum combination is likely to vary depending on the type of surgery and a range of patient factors (comorbidities, pre-existing pain, analgesics used, genetics, and 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 about 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

There are several research gaps that must be addressed to improve perioperative pain management. This approach might also contribute to addressing the wider societal problem of chronic opioid use. We have highlighted the specific research gaps that relate to the focus of this paper. First, there is a need to identify additional analgesic approaches, including those that enhance endogenous pain control mechanisms. This will require improved mechanistic understanding of endogenous opioid systems. There is some progress in this area in the preclinical field, as outlined earlier in this paper, but translation to the clinical setting is required.

Second, to understand the effect of perioperative 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 will 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 understanding of the effect of perioperative management on long-term health outcomes. Approaches to ensure that these data are robust and accurate need to be refined. Other alternatives include developing research resources by national and international collaboration (such as the UK Biobank project). Both approaches are likely to require collaboration between policy makers, clinicians, and academics.

Third, to understand and modify risk factors to opioid use at an individual level. The use of a precision medicine approach to identify high-risk individuals and evaluate targeted, individualised strategies is needed. This might 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 not surprising because of the key role that endogenous opioids have in pain processing at all levels. Better understanding of the effects of opioids at neurobiological, clinical, and societal levels is required to improve future patient care.

Contributors

All authors contributed to the review design, literature search, writing, draft revisions, and final approval of the paper.

Declaration of interests

We declare no competing interests.

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