Postoperative pain management and opioids 1

Transition from acute to chronic pain after surgery

Paul Glare, Karin R Aubrey, Paul S Myles

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.

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

Pain Management Research Institute, University of Sydney, Sydney, NSW, Australia (P Glare MBBS, K R Aubrey PhD); **Kolling Institute, Royal North Shore Hospital, St Leonards, NSW, Australia** (K R Aubrey); **and Department of Anaesthesiology and Perioperative Medicine, Alfred Hospital, Melbourne, VIC** (Prof P S Myles DS)

Correspondence to:
Prof Paul S Myles, Department of Anaesthesiology and Perioperative Medicine, Alfred Hospital, Melbourne, VIC 3004, Australia
p.myles@alfred.org.au

	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]
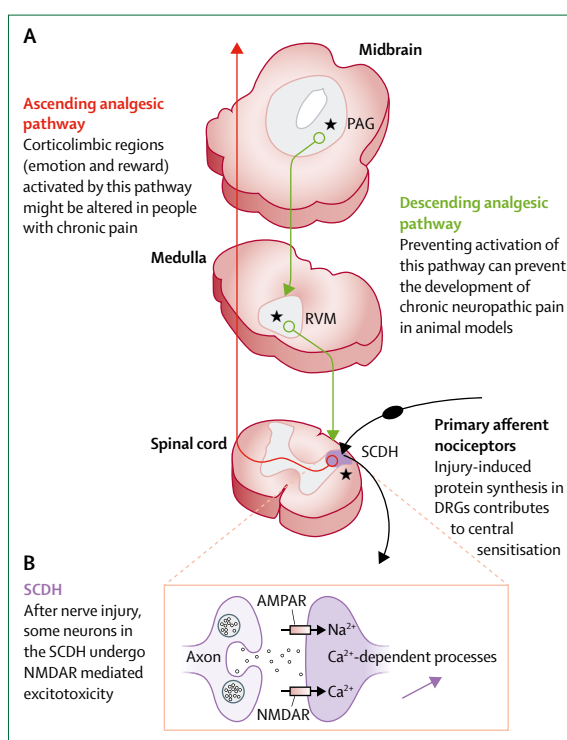

Figure 1: Neural pathways for pain
Fundamental changes to neuronal phenotypes and brain circuits occur when pain becomes chronic. These changes can alter sensory, emotional, and motivational centres of the brain and interfere with the action of traditional analgesic medications. A complete understanding 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

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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.

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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.

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),

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 nore-pinephrine reuptake inhibitors such as duloxetine and
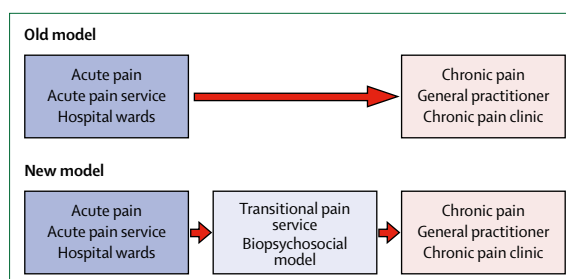

Figure 2: A transitional pain clinic model
Care in hospital and after discharge pathways.

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 sub-groups of patients with CPSP are most likely to benefit.

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 con-clusive 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]

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