Strategies Aimed at Preventing Chronic Post-surgical Pain: Comprehensive Perioperative Pain Management after Total Joint Replacement Surgery

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ABSTRACT

Purpose: Chronic post-surgical pain (CPSP) is a frequent outcome of musculoskeletal surgery. Physiotherapists often treat patients with pain before and after musculoskeletal surgery. The purposes of this paper are (1) to raise awareness of the nature, mechanisms, and significance of CPSP; and (2) to highlight the necessity for an inter-professional team to understand and address its complexity. Using total joint replacement surgeries as a model, we provide a review of pain mechanisms and pain management strategies.

Summary of Key Points: By understanding the mechanisms by which pain alters the body's normal physiological responses to surgery, clinicians selectively target pain in post-surgical patients through the use of multi-modal management strategies. Clinicians should not assume that patients receiving multiple medications have a problem with pain. Rather, the modern-day approach is to manage pain using preventive strategies, with the aims of reducing the intensity of acute postoperative pain and minimizing the development of CPSP.

Conclusions: The roles of biological, surgical, psychosocial, and patient-related risk factors in the transition to pain chronicity require further investigation if we are to better understand their relationships with pain. Measuring pain intensity and analgesic use is not sufficient. Proper evaluation and management of risk factors for CPSP require inter-professional teams to characterize a patient's experience of postoperative pain and to examine pain arising during functional activities.

Key Words: chronic post-surgical pain, inter-professional teams, multi-modal analgesia, preventive analgesia, total joint replacement

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RÉSUMÉ

Objectif : La douleur chronique postopératoire est une conséquence fréquente de la chirurgie musculosquelettique. Les physiothérapeutes traitent souvent les patients qui ressentent de la douleur avant et après ce type d'intervention. L'objectif de cet article est (1) de sensibiliser à la nature, aux mécanismes et à l'importance de ce type de douleur chronique et (2) de souligner la nécessité, pour une équipe interprofessionnelle, de comprendre et d'en maîtriser la complexité. Avec comme modèle les chirurgies de remplacement d'une articulation, nous avons analysé les mécanismes de la douleur et les stratégies pour sa gestion.

Résumé des principaux points : En comprenant les mécanismes par lesquels la douleur affecte les réponses physiologiques normales à une intervention chirurgicale, les cliniciens ont ciblé de manière sélective les patients souffrant de douleur postopératoire à l'aide de stratégies de gestion multimodales. Les cliniciens ne devraient pas déduire que les patients qui reçoivent de multiples médicaments ont un problème avec la douleur. L'approche moderne consiste plutôt à gérer la douleur à l'aide de stratégies préventives qui visent à réduire l'intensité de la douleur postopératoire aiguë et à minimiser les risques de développement de douleur chronique postopératoire.

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Conclusions : Les rôles des facteurs de risques biologiques, chirurgicaux, psychosociaux et liés aux patients dans la transition de la chronicité de la douleur devront faire l'objet d'autres recherches si nous souhaitons mieux comprendre leurs relations avec la douleur. Mesurer l'intensité de la douleur et l'utilisation d'analgésiques est insuffisant. Une évaluation et une gestion adéquates des facteurs de risques de douleur chronique postopératoire exigent que les équipes interprofessionnelles caractérisent l'expérience de la douleur postopératoire chez les patients et se penchent sur la douleur qui survient lors des activités fonctionnelles.

Mots clés : analgésie multimodale, analgésie préventive, douleur chronique postopératoire, équipes interprofessionnelles, remplacement total d'une articulation

INTRODUCTION

The majority of patients who undergo musculoskeletal surgery heal within a few months and return to their baseline functional status or to an improved level of functioning. However, a surprisingly large percentage continue to have significant pain after surgery, and as many as 30% may progress to develop chronic post-surgical pain (CPSP).^{1,2} These statistics are of concern, given the escalating demand for total hip- and knee-joint replacement surgeries and the perception that for patients with severe pain and disability due to osteoarthritis, this treatment option will relieve pain and improve function. Recently, considerable attention has been directed to the challenging problem of how best to manage pain in these patients.

Total hip- and knee-joint arthroplasty (THA and TKA) is associated with considerable pre- and postoperative pain.²⁻⁵ Unrelieved postoperative pain may increase the risk of delayed and/or sub-optimal functional recovery⁶ and the development of chronic pain syndromes.⁷ Because surgical techniques and prostheses have significantly improved, total joint arthroplasty (TJA) has emerged as the treatment of choice to reduce pain and improve function in patients with hip or knee osteoarthritis.⁸⁻¹² The US National Institutes of Health Consensus Panel and multiple Canadian federal and provincial panels have established that for persons suffering from intractable and persistent knee or hip pain and disability, TKA or THA is a safe and cost-effective therapy that restores mobility and alleviates discomfort.¹³ In the decade between 1991 and 2000, the number of primary THA and TKA surgeries more than doubled in the United States, the United Kingdom, and most Western countries that maintain registries of such surgeries, including Canada.¹⁴⁻¹⁹ However, there is growing recognition that up to 33% of patients report no functional improvement²⁰⁻²³ and between 10% and 30% report no improvement (or a worsening) of pain following THA or TKA.^{7,24}

This paper outlines typical strategies used to manage acute pain and thereby facilitate functional recovery after surgery. Simply monitoring analgesic use and pain scores after surgery does not suffice to capture the complexity of acute postoperative pain and its possible relationship to development of CPSP. The involvement of an interdisciplinary team in the postoperative recovery

of patients and the need to assess dynamic (movement-evoked) pain are also discussed. By managing acute pain aggressively, many physicians hope to decrease the development of CPSP; unfortunately, there is a paucity of data to support this idea. Finally, we discuss the underlying physiological mechanisms and risk factors that contribute to the development of chronic post-surgical pain.

Physiology of Post-surgical Pain

The classic pain pathway has been described as a neuronal signal that begins in the periphery from an injury or a noxious event and is transmitted via nociceptive receptors through the spinal cord, then upward to the brain.²⁵ Nociceptive sensory neurons transduce physical noxious energy into an electrical signal (i.e., action potentials), which then transmits the location and intensity of the noxious stimulus via the spinal cord to the brain.²⁶ This classic view of pain sensation, however, fails to integrate the role of the cerebral cortex with respect to pain perception and control.²⁷

After a surgical incision, inflammatory mediators released by damaged tissue trigger an inflammatory cascade. This inflammatory response reduces the threshold and increases the responsiveness of nociceptors (sensory receptors on C fibres and A δ fibres) to subsequent input in the damaged tissue, a phenomenon known as *peripheral sensitization*.^{28,29} The body's neurophysiological response to any insult, including surgery, may initially serve a protective function (i.e., pain limits further use) and promote healing. It is now known that a similar sensitization processes can also occur more centrally as a result of the "afferent barrage" induced by activation of nociceptors in response to surgery. The term "central sensitization" refers to an alteration in the response properties of central neurons (e.g., in the dorsal horn of the spinal cord); features of central sensitization include an increased responsiveness to activation, reduced threshold, expanded receptive fields, and spontaneous activity following injury,^{30,31} all of which contribute to increased pain after surgery. The underlying mechanisms responsible for the development of CPSP have yet to be determined; however, it is postulated that blocking or blunting peripheral and central sensitization may inhibit the processes that can lead to the development of CPSP.²⁸ The mechanisms of peripheral and central

sensitization that initially are protective may become maladaptive, with deleterious consequences, and much more resistant to treatment.²⁸

Post-surgical pain arises predominantly from two distinct processes: nociception (C fibre and A δ primary sensory neurons, which respond to intense thermal or mechanical stimuli)³² and inflammation, which is a consequence of trauma to peripheral tissues (i.e., detection of inflammation by nociceptors).²⁸ Dysfunctional pain, such as neuropathic pain that results from direct injury to the nervous tissue (e.g., nerve transection),³³ is also present in the acute postoperative period. While most neuropathic pain resolves with time,³⁴ in a subset of patients the acute neural damage from surgery can transition to chronic neuropathic pain that is often resistant to treatment. These types of injuries can result in long-term changes in the sensitivity of the nervous system, such that the intensity of subsequent stimuli necessary to induce pain is reduced (i.e., the patient develops a lower pain threshold).²⁶

It is now accepted that general anaesthesia may attenuate but does not entirely block transmission of the afferent injury barrage of signals from the periphery to the spinal cord and brain.³⁵ Moreover, systemic opioids may not provide a sufficiently dense blockade of spinal nociceptive neurons to prevent central sensitization.³⁶ The clinical significance of these findings for patients who receive general anaesthesia during surgery is that although they are unconscious, the processes leading to sensitization of dorsal-horn neurons remain largely unaffected by general anaesthesia or routine doses of opioids.

For many years, the primary modality used for postoperative pain has been opioid-based analgesia. However, the side effects of opioid-based analgesics—which include nausea, vomiting, sedation, pruritus, constipation, urinary retention, and respiratory depression³⁷—often impair patients' progress and recovery after surgery. The increased morbidity associated with opioid-only strategies and the fact that opioid medications tend not to be effective at relieving movement-evoked pain have created a movement in anaesthesiology to adopt multi-modal analgesic strategies to manage preoperative, intra-operative, and postoperative pain. These multi-modal strategies are often implemented throughout the perioperative stay (i.e., across the three phases of the hospital stay: preoperative, intra-operative, and postoperative).

Multi-modal Analgesia

With advances in the understanding of the pathophysiology of pain, multi-modal analgesia has become the standard of practice to treat moderate to severe post-surgical pain following orthopaedic surgery.³⁸ This practice involves the use of different classes of analgesic

agents, with different routes of administration, to (1) provide superior pain relief at rest and with movement, (2) reduce opioid consumption, and (3) reduce analgesic-related adverse effects.^{38,39} Many clinical trials have demonstrated the effectiveness of multi-modal analgesia; however, positive results have not been readily translated into clinical practice.^{40,41} Although single-agent therapy may attenuate central nociceptive processing, multi-modal analgesic therapy is more effective, and is often associated with fewer side effects, than high-dose, single-agent opioid therapy.^{42,43} As discussed below, empirical evidence derived from clinical trials shows that the use of multi-modal analgesic therapy using a combination of analgesic agents, each with a different mechanism of action, is effective in blocking the various inputs/receptors related to the neural and inflammatory processes.^{44–47} For example, the results of two recent studies have shown good control of acute pain with the use of multi-modal pain regimens after THA or TKA.^{44,48} Multi-modal pain regimens of gabapentin, non-steroidal anti-inflammatories (Celebrex), acetaminophen, and regional anaesthesia were effective in controlling perioperative pain and decreasing perioperative opioid use.^{44,48} More data are needed to determine whether similar multi-modal pain regimens with regional anaesthesia—an anaesthetic that affects a large part of the body, such as a limb, which is often achieved with central-neuraxial anaesthesia (i.e., spinal/epidural anaesthesia) and/or peripheral nerve blocks—reduce the time course of recovery and/or maximize functional recovery of patients following major orthopaedic surgery, such as THA or TKA.

PREVENTIVE APPROACHES TO MINIMIZING ACUTE AND CHRONIC POST-SURGICAL PAIN

Pre-emptive Analgesia

Pre-emptive analgesia has been defined as preoperative anti-nociceptive treatment that prevents the establishment of surgery-induced central sensitization and heightened postoperative pain intensity.⁴⁹ The classic design used to evaluate the efficacy of pre-emptive analgesia requires two groups of patients to receive identical treatment before or after surgery; the only difference between the two groups is the timing of administration of the analgesic agent relative to incision. This view assumes that the intra-operative nociceptive barrage makes a greater contribution than the postoperative nociceptive barrage to central sensitization and postoperative pain. The expectation has been that the group that received treatment before surgery will have less pain than the group that received treatment after surgery.

This view of pre-emptive analgesia is too restrictive and narrow,^{50–52} however, in part because (1) we know that sensitization is induced by factors other than the

peripheral nociceptive barrage associated with incision and subsequent noxious intra-operative events, and (2) we do not know the relative extent to which pre-, intra-, and postoperative peripheral nociceptive inputs contribute to central sensitization and postoperative pain.

The almost exclusive focus in the literature on this narrow view of pre-emptive analgesia has had the unintended effect of diverting attention away from other clinically significant findings that do not conform to what has become the accepted definition of pre-emptive analgesia.⁵³ The classic two-group research design does not allow for other equally plausible alternatives that have received empirical support in the pain and anaesthesia literatures.^{54–56} Previous studies suggest that better pain relief may be achieved when the analgesic intervention is started after incision and, potentially, after surgery (i.e., in the context of an unchecked peripheral nociceptive injury barrage during surgery). Recently, the concept of *preventive analgesia* has replaced the emphasis that the narrow view of pre-emptive analgesia placed on the timing of analgesic administration.

Preventive Analgesia

A broader approach to the prevention of postoperative pain has evolved that aims to minimize the deleterious immediate and long-term effects of noxious perioperative afferent input.⁵³ The focus of *preventive analgesia* is not on the relative timing of analgesic or anaesthetic interventions but on attenuating the impact of the peripheral nociceptive barrage associated with noxious preoperative, intra-operative, and/or postoperative events/stimuli. These stimuli induce peripheral and central sensitization, which increase postoperative pain intensity and analgesic requirements; preventing sensitization will reduce pain and analgesic requirements. Preventive analgesia is demonstrated when postoperative pain and/or analgesic use are reduced beyond the clinical duration of action of the target agent, which has been defined as 5.5 half-lives of the target agent.⁵³ This requirement ensures that the observed effects are not analgesic effects.^{50,53,57}

Only recently have clinical trials begun to examine the effects of perioperative interventions well beyond the surgical period (i.e., looking for a preventive effect). Long-term follow-up of patients several weeks, months, or years after surgical intervention is necessary in order to test for the preventive effects of a perioperative intervention.

ANALGESIC AGENTS COMMONLY USED FOR PERIOPERATIVE PAIN CONTROL

Opioids

Opioid medications such as fentanyl, morphine, meperidine, hydromorphone, and oxycodone are com-

monly used worldwide to treat postoperative pain. Opioid medications remain the mainstay of perioperative analgesia because they are best suited for moderate to severe pain and have been demonstrated to be effective across a broad spectrum of conditions, most likely because of their supraspinal, spinal, and peripheral sites of action. Standard perioperative pain management often relies on opioids as the primary pain medication. As noted above, however, opioids tend to be ineffective for severe pain that is associated with movement, and they have significant short-term side effects (including nausea, vomiting, sedation, pruritus, constipation, urinary retention, and respiratory depression),³⁷ factors that can hinder a patient's rehabilitation.

Studies have demonstrated that clinically relevant tolerance to opioids can occur within hours of their intra-operative use.^{58,59} Intra-operative development of tolerance may reduce the postoperative analgesic efficacy of opioids, delay discharge from hospital,⁶⁰ and ultimately lead to the development of long-term tolerance, which can result in physical dependence and addiction.

Many of the postoperative pain strategies practised by anaesthesiologists rely on other classes of medications to decrease the amounts of opioid analgesics consumed by patients. Implementing a multi-modal regimen at the outset can diminish the unwanted side effects of opioid analgesics.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The analgesic effects of NSAIDs have been attributed to their anti-inflammatory properties with respect to inhibiting the synthesis of prostaglandins.⁶¹ Prostaglandin synthesis is essential for the generation of inflammatory pain, and this depends not only on prostaglandin production at the site of inflammation but also on the actions of prostaglandins synthesized within the central nervous system. Prostaglandins derive from arachidonic acid liberated from phospholipids in the cell membrane by the action of phospholipase A₂ (PLA₂) enzymes.⁶² Cyclooxygenase (COX) catalyzes the first two reactions of the prostaglandin pathway. The identification of two COX isoforms, COX-1 and COX-2, led to intense efforts to characterize the relative contribution of each isoform to prostaglandin production in specific situations⁶² and to the development of specific COX-2 selective inhibitors, as COX-2 is an enzyme responsible for inflammation and pain.

The finding that the inflammatory cascade caused by tissue injury can be decreased at the periphery and blunted at the level of the spinal cord has increased the use of NSAIDs as an adjunct for the treatment of postoperative pain.^{63,64} Bioavailability of NSAIDs is higher for oral and intravenous than for rectal administration; the former routes of administration are therefore

preferred postoperatively.⁶⁵ However, NSAIDs are not widely used because of their potential adverse effects, which include gastric ulceration or haemorrhage, renal dysfunction, and platelet inhibition. It is clear that NSAIDs should be used with caution in patients who have a history of renal dysfunction, sepsis, end-stage liver disease, or cardiac disease. Evidence has demonstrated that the short-term use of non-selective NSAIDs (e.g., ketoprofen/ibuprofen) is safe with respect to gastrointestinal complications.^{66,67} In terms of bone repair, animal data had postulated a link between impaired bone fusion and the use of NSAIDs,⁶⁸ but clinical data have not supported such a link.^{69–71} A 2-year randomized study demonstrated that a 3-week postoperative regimen of celecoxib (Celebrex) did not affect prosthesis fixation after TKA.⁷¹ More studies examining the safety of NSAIDs are needed to evaluate the effects of reducing the inflammatory process on other tissues, such as muscle and tendon repair, as well as functional outcomes following arthroplasty surgery. While it seems logical that resolving inflammation should improve tissue-repair processes, there is conflicting evidence from animal models of skeletal muscle and tendon injury and repair that challenges the notion that prolonged use of anti-inflammatories, particularly beyond the acute inflammatory phase, is beneficial.^{72–74} In an animal study using prolonged blockade of inflammation by non-selective NSAIDs throughout the perioperative period and beyond, researchers observed an increase in rearing (standing on hind limbs) and ambulatory behaviour in rats 1–3 days post knee surgery.⁷³ The increased spontaneous activity level suggests that the blockade was effective; whether a similar effect would be seen in humans remains unknown.

COX-2 selective inhibitors have been developed to target the COX-2 enzyme while sparing the COX-1 enzyme. The only available COX-2 agent in North America is celecoxib (Celebrex). Studies suggest that COX-2 selective inhibitors have similar analgesic effects as non-selective NSAIDs but do not affect platelet function. This reduces the risk of perioperative bleeding and means that COX-2 selective inhibitors can safely be given preoperatively.^{69,75–77} Of particular importance in the arthroplasty population is the fact that COX-2 selective inhibitors do not inhibit bone healing.⁷⁸ However, their effects on muscle-tissue and connective-tissue healing, which are important for regaining full function postoperatively, remain unknown.

The choice of NSAID (i.e., non-selective or COX-2 specific) will often be determined by factors such as available pharmacy formulations, cost, and patient tolerance. In the postoperative setting, the addition of an NSAID to a post-surgical regimen is often influenced by the severity of the patient's acute pain. Arthroplasty pain has been well described as moderate to severe in the acute 48-hour post-surgical period.¹ The selective

COX-2 inhibitors continue to demonstrate a good analgesic and anti-inflammatory profile,⁷⁹ while sparing patients the non-desirable effects of the COX-1 agents. Celecoxib seems to be an ideal adjunct within post-surgical multi-modal analgesic regimens after orthopaedic surgery.

Acetaminophen

Acetaminophen is a widely used analgesic and antipyretic drug that is available over the counter; it is remarkably safe and is often used for mild to moderate pain.⁸⁰ The most common indications are for headache, migraine, fever, menstrual pain, toothache, dental pain, muscular and joint pain, and neuralgia.^{81–84} The anti-inflammatory effects of acetaminophen are much weaker than those of NSAIDs;⁸⁵ acetaminophen lacks anti-rheumatic effects, which presumably reflects the modest peripheral inhibiting effect on prostaglandin synthesis produced by this drug.^{86,87} Conversely, acetaminophen has been shown to inhibit the action of endogenous pyrogens on the heat-regulating centres in the brain by blocking the formation and release of prostaglandins in the central nervous system.⁸⁸ Some researchers postulate an entirely different central mechanism of action (i.e., a COX-3 pathway). The COX-3 pathway would strongly inhibit central prostaglandin synthesis in the hypothalamus and decrease prostaglandin E in cerebrospinal fluid, ultimately producing the analgesic and antipyretic effects.^{89–91} There is ongoing research to elucidate the COX-3 mechanism of action of acetaminophen.

Although acetaminophen has a very good safety profile, overdoses, either deliberate or accidental, are not uncommon. The recommendation is that adults or children over 12 years of age can be given 500 mg to 1 g of acetaminophen every 4–6 hours up to a maximum of 4 g in any 24-hour period. Adverse events rarely occur within therapeutic doses, although there have been reports of increased liver enzymes with long-term use at the higher doses.⁹²

Two systematic reviews have demonstrated the beneficial effects of acetaminophen versus placebo to treat postoperative pain.^{93,94} Using a dose-response study design, McQuay and Moore demonstrated that 1 g of acetaminophen produced greater benefits than a dose of 600–650 mg, with a number needed to treat (NNT) of 9.⁹⁵ When acetaminophen was combined with codeine, the NNT decreased to 2.2.⁹⁵ One systematic review that compared acetaminophen versus NSAIDs revealed mixed results;⁹⁶ the authors concluded that the treatment of postoperative pain was superior when the agents were combined than when either single agent was administered alone. Acetaminophen's efficacy in treating mild to moderate pain, combined with its relatively benign side-effect profile (no gastric irritation or platelet aggregation effects), explains why it continues to be widely used as part of postoperative multi-modal pain regimens.

***N*-Methyl-D-aspartate (NMDA) Antagonists**

NMDA antagonists became the focus of intense research upon the discovery of a receptor-ion channel complex that was found to play an important role in the induction and maintenance of central sensitization and pathological pain.^{97,98} In particular, ketamine and dextromethorphan have been investigated with respect to their ability to provide postoperative analgesia.^{99,100} Low doses of ketamine have been shown to reduce opioid requirement, prolong opioid/epidural analgesia, and improve pain relief.^{57,101} Ketamine was originally developed as a general anaesthetic; however, because of significant psycho-mimetic side effects, its perioperative use declined.¹⁰² Recently, low-dose regimens (in the range of 0.25–0.5 mg/kg as an initial bolus followed by 50–500 µg/kg/h) have been proposed as an adjuvant for postoperative analgesia and for the reduction of exogenous opioid-induced hyperalgesia.¹⁰³ Preventive effects (improved mobility well beyond 5.5 half-lives of the agent) of ketamine use have been demonstrated after TKA.^{99,104} Patients who were given continuous infusions of ketamine (3 µg/kg/min) from induction of anaesthesia until 48 hours after surgery demonstrated improved maximal active knee flexion 6 days post surgery. This improved range of motion was maintained at 6 weeks and 3 months post surgery compared to patients who received placebo treatment.¹⁰⁴ Despite evidence that NMDA antagonists result in reduced postoperative opioid requirements and pain intensity within many other surgical populations,^{105–107} ketamine and dextromethorphan are not commonly used as part of multi-modal analgesic regimens. One of the clinical barriers to their use is that ketamine lacks an oral formulation. In some countries, an oral formulation of dextromethorphan has become available; pain experts have proposed that this oral compound could be used to maintain NMDA receptor blockade after discharge home.¹⁰⁸ More research into the effectiveness of dextromethorphan is needed prior to its administration outside the hospital setting as an adjunct for pain.

Anticonvulsants

Gabapentin and pregabalin are believed to operate as $\alpha 2\delta$ -sub-unit voltage-dependent calcium channel blockers,¹⁰⁹ but their mechanisms of action remain incompletely understood. Gabapentin is a structural analogue of gamma-amino butyric acid and was introduced into clinical practice as an anticonvulsant drug; pregabalin is a newer $\alpha 2\delta$ ligand introduced as a core treatment for neuropathic pain. Recent basic science research has demonstrated that gabapentin increases tonic inhibitory currents in murine hippocampal neurons.¹¹⁰ Work is ongoing with respect to elucidating the possible central role of the gabapentinoids in the mammalian central nervous system. It is likely that there are both peripheral

and central mechanisms that mediate the clinical effects of these medications.

Over the past 8 years, many trials have examined the efficacy and effectiveness of gabapentin in treating acute post-surgical pain. The surgical populations studied include abdominal or pelvic surgery,^{111–118} musculoskeletal surgery,^{119–126} head and neck surgery,^{127–129} breast surgery,^{130–133} varicocele surgery,¹³⁴ thoracic surgery,¹³⁵ and, recently, cardiac surgery.¹³⁶ Of these randomized controlled trials, most consisted of a single dose of gabapentin given prior to surgery. Only four of the above trials failed to demonstrate a decrease in pain scores or an opioid-sparing effect in the early post-surgical period.^{112,119,120,124} Recently, Mathiesen et al. demonstrated the effectiveness of pregabalin in reducing opioid consumption after THA.¹³⁷ Several meta-analyses have confirmed that these anticonvulsants reduce both postoperative opioid use and postoperative pain scores.^{138–140}

Most trials thus far have compared gabapentin to a placebo. Gilron et al.¹¹³ and Turan et al.¹¹⁸ published studies in which gabapentin and celecoxib were given together and compared to each agent in isolation. Both studies demonstrated similar results: the group that received the multi-modal intervention showed superior opioid-sparing and pain-reducing effects relative to the single-agent groups. Similar results have been demonstrated with respect to the effectiveness of multi-modal analgesia after THA or TKA.^{44,48} A recent study demonstrated the effectiveness of continuing gabapentin for 4 days into the postoperative period, in conjunction with peripheral nerve blocks and celecoxib. This combined treatment regimen resulted in a significant increase in active assisted knee flexion during a standardized rehabilitation programme.⁴⁴ One of the challenges with such trials is the use of impairment-based outcomes (e.g., range of motion) that are not necessarily associated with functional abilities (e.g., ability to climb stairs).

Osteoarthritis (OA), the most common reason for TKA, accounts for more difficulty with climbing stairs and walking than any other disease.^{141,142} Since one of the primary goals of TKA is to improve physical function, this provides an ideal model to study the effects of gabapentin on functional outcomes. While many trials have demonstrated reductions in movement-induced post-surgical pain,^{113,116,118,121,127,130,132} whether this reduction translates into accelerated recovery and/or improved functional outcomes remains unknown. Future trials must evaluate the effects of gabapentin and pregabalin on recovery following TJA within the context of multi-modal analgesia. Outcomes for such trials should include both self-report and performance-based measures of physical function,^{143,144} such as the 6-minute walk test,^{145,146} the timed up-and-go test,^{147,148} and a timed stair test,^{21,23,149} all of which have demonstrated reliability and sensitivity to change within the TJA population.¹⁵⁰

Local Anaesthetics

Local anaesthetic solutions have been used to provide anaesthesia for centuries. Today, the use of local anaesthesia continues to be a very important adjunct to decrease pain, opioid consumption, and opioid-related side effects.¹⁵¹ Regional anaesthesia (which uses local anaesthetic solutions) is an integral part of orthopaedic anaesthesia practice. As part of anaesthetic care, local anaesthetics have been shown to facilitate early mobilization and discharge.^{152,153} Local anaesthetic solutions (e.g., bupivacaine and lidocaine) are commonly used neuraxially (spinal/epidural) and have become popular in some centres for intra-articular use.

Spinal/epidural anaesthesia has become the anaesthetic modality of choice in centres that specialize in lower-limb arthroplasty. Such centres have developed specialized areas where patients receive their surgical anaesthesia (spinal/epidural) and peripheral nerve blocks (femoral and/or sciatic nerve blocks/catheters) prior to entering the operating room. This is one of the factors that has enabled increased surgical volumes and decreased surgical wait times in Ontario.¹⁵⁴ Prior to implementation of these specialized preoperative pain-management areas, anaesthesiologists were challenged to prepare patients undergoing orthopaedic procedures with the appropriate regional anaesthesia block, often because of time pressures in the operating room. The addition of specialized preoperative anaesthesia block areas has increased the availability of intrathecal/spinal anaesthesia and regional anaesthesia blocks for use with patients undergoing major orthopaedic surgery. The mandate to reduce wait times and increase surgical volumes has also been the impetus for closer collaboration among anaesthesiologists, physical therapists, nurses, and surgeons to optimize efficiency while maintaining safe mobilization of patients undergoing THA or TKA.

Local anaesthetics injected into the intra-articular space have been shown to improve pain scores, reduce opioid consumption, and facilitate functional recovery and mobilization after knee arthroscopy.¹⁵⁵ Although the duration of pain relief may be shorter than with peripheral nerve catheters and neuraxial analgesia, this technique may play a larger role in ambulatory orthopaedic day surgeries (e.g., arthroscopy). Ongoing studies are investigating the effectiveness of intra-articular injections for patients with THA and TKA.

Regional Anaesthesia Adjuncts after Lower-Limb Musculoskeletal Surgery

Single-Shot Peripheral Nerve Blocks

Femoral and sciatic nerve blocks remain very popular after TKA.^{156,157} The femoral nerve innervates the anterior compartment of the knee, while the sciatic nerve innervates the posterior compartment. In patients who receive femoral nerve blocks only, posterior knee

compartment pain can be problematic, leading some clinicians to recommend that administering both blocks provides superior pain relief after TKA.¹⁵⁷ For foot and ankle surgery, popliteal fossa nerve blocks (which target the sciatic nerve as it passes below the knee) provide analgesic success with minimal side effects.¹⁵⁸ The duration of neural blockade can be quite variable. Block duration is determined by the properties of the local anaesthetic used, the concentration of the local anaesthetic, and the volume injected. A longer-acting solution of ropivacaine 0.5% (20 mL), deposited adjacent to each nerve, will produce a mean anaesthetic duration of action of 15 hours.¹⁵⁹ Occasionally it becomes difficult to predict the level of motor impairment that accompanies single-shot nerve blocks. This is a significant consideration for patient safety if ambulation on postoperative day 0, or early on postoperative day 1, is desirable. The inability to accurately predict the density of neuronal blockade that will be experienced by patients (i.e., a good sensory nerve block with minimal motor impairment) is the reason that continuous peripheral nerve catheters have increased in popularity and use.

Continuous Peripheral Nerve Catheters

Through the placement of a catheter in the perineural space, the duration of analgesia can be prolonged and the density of the block better managed by infusion of the anesthetics.^{160,161} Most studies comparing this method directly to intravenous patient-controlled analgesia (PCA) have demonstrated superior pain relief at rest and with movement, better postoperative knee flexion, and earlier discharge.^{162,163} Unfortunately, the increased cost of this technique and lack of expertise in placing peripheral nerve catheters often limits their use. Whenever peripheral nerve techniques (either single shots or catheters) are used, it is very important that anaesthesiologists and physiotherapists engage in dialogue in order to reach rehabilitation goals and avoid the delay in functional recovery that can be caused by dense motor blockade.

FEAR, ANXIETY, AND PAIN AFTER SURGERY

Current bio-psychosocial models propose that pain-related fear- and anxiety-based constructs are critical to the process(es) leading to the development of chronic pain and functional disability.^{164–167} Recognizing the importance of pain-related fear and anxiety in the transition to chronicity, this section describes how these constructs may be relevant to the experience of acute and chronic pain and their impact on physical function in post-surgical patients.

The most common emotions experienced by patients scheduled for major surgery are fear and anxiety. These are two distinct emotions, although they have a good

deal in common. The situations and factors that produce them and the subjective states associated with these emotions are often similar; one of the main differences between fear and anxiety involves the temporal relation to the presentation of the perceived threat: *fear* is defined as the emotional response to a present, ongoing threat, while *anxiety* is the response to a potential or future threat.¹⁶⁸ Thus, the actions that accompany fear and anxiety will also differ, with escape and avoidance behaviours associated with the former and latter respectively.

Avoidance behaviour is usually motivated by anxiety. Many patients with pain are afraid that movement will cause re-injury and further pain.^{169,170} For example, in the days and weeks following surgery, it is common for pain to be exacerbated by movement; depending on the location of the incision, deep breathing, coughing, laughing, and getting in and out of bed may substantially increase pain. In anticipating pain, many patients become anxious about the consequences of moving about, and may therefore avoid activities altogether.

Understanding the personal meaning of the fear or anxiety is important. Patients may believe that if they sit up or walk around, their stitches will break and the wound will split open; they may also worry that these activities will cause permanent internal damage. Other patients simply fear the increase in pain that is associated with activity; they may feel helpless in the presence of intense pain, or they may feel dependent on the nursing staff for pain relief. Apprehension about moving about after surgery is based on authentic feedback that has taught patients that activity causes increased pain. However, it is the misinterpretation of activity and pain as harmful that engenders avoidance behaviours, which may set the stage for the negative consequences of decreased activity and increased pain and disability. It is important that patients understand the difference between *hurt* and *harm* and that physiotherapists and anaesthetists work collaboratively to minimize exposure to pain that may have enduring effects.

While avoidance by means of social withdrawal and inactivity may reduce pain, particularly in the early recovery phase, these behaviours have negative long-term consequences. Such fear-avoidance beliefs include expectations about the consequences of certain physical actions (e.g., physical activity, work) on pain.¹⁷¹ Avoidance behaviours (e.g., guarding, limping, social withdrawal) may be part of coping with ongoing pain or anticipated increases in pain; however, some of these behaviours may also represent maladaptive ways of coping with concurrent life difficulties. Unpleasant work obligations or household chores, marital strife, and interpersonal difficulties may thus be avoided by the person in pain. Those pain behaviours that serve the dual purpose of avoiding expected flare-ups in pain and evading other unpleasant life events are at high risk of becoming

entrenched, thanks to multiple sources of negative reinforcement.¹⁷²

Patients' fear-avoidance beliefs and negative expectations about the consequences of activity are meant to reduce anticipated increases in pain through avoidance. Avoidance behaviours tend to increase in frequency as pain becomes chronic, so that pain behaviours and pain intensity become increasingly decoupled.¹⁷³ This asynchrony sets the stage for reduced self-efficacy beliefs and further activity avoidance.¹⁷⁴ Thus, when attempting to gain control over their pain through avoidant coping, patients actually report an increasing loss of control over their pain. Self-management programmes focused on behavioural exposure and non-avoidance lead to improved self-efficacy and a reduction in preoccupation with pain as patients acquire increasingly realistic appraisals of the relationship between pain and behaviour.¹⁷⁴

Although use of avoidant cognitive coping strategies for pain may be beneficial when pain is acute, long-term use of these strategies is associated with impaired psychosocial functioning, increased pain and disability, and loss of employment. Avoidant coping strategies may be adaptive in the early period following an injury, because they minimize the pain experienced and may reduce the risk of exacerbation through further injury. Once healing has occurred, however, these strategies become maladaptive, because they promote continued isolation, inactivity, and faulty reality testing.

Recent controlled studies¹⁷⁵ and case-report trials^{175–177} have shown that pain-related fear can be effectively treated by *in vivo* exposure, whereby patients are exposed to fear-eliciting and hierarchically ordered physical movements. Results showed concomitant reductions in catastrophic thinking, pain intensity, and pain disability. To the best of our knowledge, studies have yet to assess the efficacy of such exposure-based treatments in patients with acute or chronic post-surgical pain.

THE TRANSITION OF ACUTE TO CHRONIC PAIN AFTER SURGERY

The incidence of CPSP varies according to the type of surgery, but even the lowest estimates are unacceptably high.¹⁷⁸ The data show that 1-year incidence ranges from a low of approximately 10%–15% following modified radical mastectomy to a high of 61%–70% for thoracotomy.¹⁷⁸ Identifying the factors that contribute to the transition from acute, time-limited post-surgical pain to chronic pathological pain is essential if we are to make progress in preventing CPSP. Research designed to identify the risk factors for transition to chronicity is at a relatively early stage. The bulk of the research is cross-sectional and associative, aimed at identifying factors correlated with the development of CPSP; few studies have used prospective, longitudinal designs to

ascertain temporal predictors of CPSP development. Finally, a handful of studies in the anaesthesia literature have attempted to manipulate hypothesized causal risk factors through administration of agents that either block acute post-surgical pain or block the downstream neuronal effects and inflammatory mediators consequent on surgery. These studies, based on recent reviews,^{53,178} confirm earlier suggestions that chronic post-surgical pain can be minimized or prevented using analgesic approaches that involve aggressive perioperative multimodal treatment; however, other studies have failed to demonstrate this benefit.^{53,178}

At present, predictors of the transition to CPSP are broadly classified as biological factors (e.g., younger age^{179,180} and female gender¹⁷⁹); surgical factors; psychosocial factors; and individual or patient-related differences.

Surgical Factors and CPSP

The following surgical factors are associated with an increased likelihood of developing chronic post-surgical pain: increased duration of surgery, low- (vs. high-) volume surgical unit, open (vs. laparoscopic or arthroscopic) surgery, herniorrhaphy, pericostal (vs. intracostal) stitches, and intra-operative nerve damage.¹⁷⁸ Whether the above factors are causally related to the development of chronic pain is not known. What these factors appear to have in common is greater surgical trauma; in particular, they point to intra-operative nerve injury as a likely causal mechanism, but this remains to be confirmed.

Psychosocial Factors and CPSP

Patients about to undergo surgery, and those in the days after surgery, are fearful and anxious about many things, including the hospital environment, being away from home, invasive medical procedures, diagnostic uncertainty, and post-surgical pain. Pain is influenced by a host of factors, such as culture, the meaning of the situation, attention-diversion and distraction, feelings of control, suggestion and placebos, and fear and anxiety.¹⁸¹ Preoperative anxiety and fear-based states have been shown to be associated with (1) the intensity of acute postoperative pain and analgesic consumption¹⁸² and (2) the development of CPSP.^{183–185} Other studies have shown that certain psychosocial factors (e.g., emotional numbing), measured following hospital discharge, are predictive of subsequent CPSP and pain disability.¹⁸⁶

Patient-Related Factors and CPSP

One of the most consistent patient-related predictors of acute and CPSP is pain itself—current or past.^{34,178,187,188} This appears to be true across various types of surgery and irrespective of time frame. The presence of pre-

operative pain, or its intensity or duration, is a risk factor for the development of severe early acute postoperative pain, acute pain days and weeks after surgery, and long-term post-surgical pain. Not only does preoperative pain predict later pain, but the severity of acute postoperative pain in the days and weeks after surgery predicts the development of CPSP (but see Katz et al.¹⁸⁶ for an exception). No other factor is so consistently related to the development of future pain problems as is pain itself. What must be determined, however, is which aspect(s) of pain is (are) predictive. There are several candidate theories for why pain predicts pain, including those that propose that pain plays a causal or associative role;¹⁷⁸ further research is required to evaluate these theories and the role played by pain and other factors in the development of CPSP.

Summary

Although the biological (female sex and younger age), surgical, psychosocial, and patient-related risk factors reviewed above temporally precede the development of CPSP and pain disability, their role as causal determinants has not been established. If the relationship is merely associative, it is likely that both the risk factor and the outcome are caused by one or more interrelated factors. The importance of establishing the nature of this relationship is obvious; some causal risk factors, once identified, may be modified or removed, thereby decreasing the risk of developing CPSP, whereas targeting associative risk factors for intervention will have no impact on the development of CPSP.

THE IMPORTANCE OF EXPANDING THE DOMAIN OF OUTCOME MEASURES

The main outcome measures in most trials of pre-emptive/preventive analgesia are pain intensity (or the presence/absence of pain) and analgesic use. It is rare to find a study that is more comprehensive in the outcome measures assessed. Recommendations for assessment of core measures and domains in clinical trials¹⁸⁹ include relevant psychological, emotional, and physical variables in addition to those routinely assessed (i.e., pain and analgesic use). Assessment of additional domains of physical function and the experience of pain during these functional activities may help to shed light on the predictors of severe acute postoperative pain, the processes involved in recovery from surgery, and the risk factors for developing CPSP.¹⁹⁰ Understanding the relationship between a patient's experience of pain and function, as well as how to reduce the development of CPSP, is critically important, particularly for patients undergoing THA or TKA.

Individuals with severe OA have often suffered months or years of unrelenting activity-related pain and, in the

later stages, considerable pain at night as well. Since there is no cure for OA, treatment strategies focus on alleviating the symptoms (e.g., pain and swelling) while maintaining optimal function. TJA has emerged as the treatment of choice for patients with severe pain from OA. While the common perception is that TJA outcomes are excellent, the reality is that between 10% and 30% of patients^{7,24} continue to experience pain and that some 20–33% report no functional improvement, even 1–2 years after replacement of the affected joint.^{20–23} Given that the presence of pain is consistently related to the development of future pain problems, perhaps these statistics are not so surprising.

We must develop better measures to evaluate pain in order to identify those at risk of developing CPSP and in order to be better able to distinguish the underlying cause of the postoperative pain (i.e., infection vs. mechanical vs. neuropathic). These measures include sensory, motor, biomechanical, psychological, and physiological markers, in addition to better characterization of the quality and quantity of pain and learned non-use of joints with OA and following TJA. The ageing of the Canadian population means that the volume of TJA procedures will continue to grow over the next few decades.^{191–193} Reducing the proportion of those patients who go on to develop CPSP following TJA will require inter-professional collaboration, particularly among anaesthesiologists, physical therapists, and orthopaedic surgeons.

SUMMARY

The transition of acute postoperative pain to pathological chronic post-surgical pain (CPSP) is a complex and poorly understood process involving biological, psychological, and social-environmental factors. The noxious effects of surgery and the demand for early and full rehabilitation compete with the beneficial effects of perioperative preventive multi-modal analgesia. These competing factors must be considered together with the interacting effect of pre-existing and concurrent pain, psychological and emotional factors, and the social environment to determine the nature, severity, frequency, duration, and risk of developing CPSP. The effectiveness of psychological management programmes for other chronic pain problems is well established; however, the development of measures to identify those at risk of developing CPSP, as well as other prevention and treatment strategies for CPSP, have not received the attention they deserve. Development and evaluation of truly multi-dimensional preventive pain-management strategies and their effects on surgical and rehabilitation outcomes for patients who require THA or TKA is long overdue. Such strategies would include not only modification of known surgical risk factors and protective pharmacotherapy but also provision of perioperative psychological pain-

management interventions aimed at preventing and treating CPSP while optimizing functional recovery through safe, early mobilization.

It is important that members of the interdisciplinary team (i.e., anaesthesiologists, surgeons, physiotherapists, psychologists, nurses, and pharmacists) recognize the many perioperative pain-management strategies available for any given patient. Designing selective, tailored, multi-dimensional pain-management regimens that address the sensitivities and needs of each individual should reduce the incidence of CPSP. For caregivers, the addition of perioperative medications/interventions should not be seen as indicating that the patient has worse pain or a “chronic pain problem”; instead, it should be welcomed as a strategy that improves functional recovery and may decrease the incidence of long-term post-surgical pain and dysfunction. Cohesive interdisciplinary teams would be better equipped to develop protocols and uncover novel information that might enable the prediction of which patients will recover uneventfully from surgery and which may go on to develop disabling CPSP. Fostering collaboration among anaesthesiologists, surgeons, psychologists, and physical therapists will provide a solid foundation for the development of future teams to investigate and effectively manage long-term pain and functional outcomes after major orthopaedic surgery.

KEY MESSAGES

What Is Already Known on This Topic

Pain is a significant health care problem, and its timely and effective management is a priority. Patients with musculoskeletal disease, such as osteoarthritis, often seek physiotherapy treatment to relieve their pain. For those who are not helped by conservative treatment, TJA is the next best alternative to alleviate pain and reduce disability. Until recently, the common perception was that THA and TKA are successful at both reducing pain and improving function; however, recent epidemiological studies have suggested that up to one-third of all surgical patients, including those post THA, develop chronic pain following surgery. While there is a growing body of literature focused on measuring function in the TJA population, very little research has been conducted to better understand and evaluate the experience and sequelae of pain in this group.

What This Study Adds

This review provides an update on the presumed pathophysiological mechanisms that contribute to the development of CPSP, including peripheral sensitization, central sensitization, and psychosocial factors. This knowledge, when combined with an understanding of the mechanisms of action of various pain medications, will enable clinicians to select patient-specific multi-

dimensional strategies to optimize management of acute post-surgical pain. Whether these strategies will be effective in reducing the incidence of CPSP after TJA remains to be seen. Optimal evaluation of the effectiveness of these multi-modal analgesic strategies is complex and requires a collaborative inter-professional team; no single discipline has the breadth and depth of understanding to manage pain effectively.

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