The burden of acute postoperative pain and the potential role of the COX-2-specific inhibitors

J. Stephens, B. Laskin, C. Pashos¹, B. Peña² and J. Wong³

Pain has been recognized as a problem of global proportions, and postoperative pain is one of the most common types of pain. Postoperative pain is acute and, although it is preventable and/or treatable, it is often undertreated. Lack of appropriate analgesic management has significant impact on clinical and economic outcomes. Negative clinical outcomes of inadequately managed acute postoperative pain include extended hospitalization, compromised prognosis, higher morbidity and mortality, and the development of a chronic pain state as a result of neuronal plasticity. Although estimating the economic burden of postoperative pain is difficult, this burden is considerable and results from direct costs due to excess health-care resource use, as well as indirect costs due to reduced patient functionality and productivity. These latter factors also have a significant adverse impact on patients’ quality of life and may be associated with the development of depression and anxiety. Thus, improved clinical outcomes are dependent not only on the availability of effective drugs but also on their appropriate utilization. A multimodal approach incorporating different drugs and techniques is effective in reducing postoperative pain but is limited by the currently available therapies. The efficacy of opioids is well established, but there are concerns about dependency, respiratory depression and side-effects, which patients often find intolerable. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective as adjunctive medication in a multimodal regimen but are associated with side-effects, such as platelet dysfunction and renal and gastrointestinal toxicity, that have special clinical significance in patients undergoing surgical procedures. Cyclooxygenase-2-specific inhibitors such as celecoxib, rofecoxib and valdecoxib, were developed to provide the efficacy of non-specific NSAIDs while limiting associated toxicity. These agents have demonstrated analgesic efficacy and an opioid-sparing effect in a variety of surgical procedures, suggesting their value as an alternative to non-specific NSAIDs. Further studies are needed to determine the impact of these drugs on clinical and economic outcomes when used in a programme of postsurgical pain management.

KEY WORDS: Postoperative pain, Pain management, Pain burden, Opioids, NSAIDs, COX-2-specific inhibitors, Outcomes.

With the identification of pain by the World Health Organization [1] as a problem of global proportions and the publication of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) pain standards [2, 3], there is increasing acceptance of pain as the fifth vital sign, on a par in significance with blood pressure, pulse and respiration [4, 5].

In contrast to chronic pain, for which no adaptive value has been demonstrated, acute pain is the normal physiological response to tissue insult or injury and has
adaptive value by serving as a warning of danger or damage. Most acute pain is either treatable or avoidable, especially when it occurs in a clinical setting. If acute pain is poorly or inappropriately treated, it may progress to chronic pain [6, 7]. Thus, effectively modulating the response to acute pain may be considered the primary step in prevention of chronic pain.

Postoperative pain is one of the most common forms of acute pain [8, 9]. Its suboptimal management has been recognized as a problem by clinicians for the past 50 yr [10–12] and has been formally identified as a public health concern by various societies and government institutions in the USA, Australia and Europe [13–16]. In 1992, the US Agency for Health Care Policy and Research developed guidelines for the management of postoperative pain in the hope of increasing awareness of the consequences of poor pain control in the postoperative setting and promoting better pain management techniques [13]. These consequences include delayed healing, longer hospitalization and the development of chronic pain, and are significant not from the patient’s perspective (decrease in functionality and quality of life) but also from the health economic perspective, by resulting in increased health-care utilization and costs.

A multimodal approach to postoperative analgesia, using a combination of agents [opiates, local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs)] and delivery techniques [patient-controlled analgesia (PCA), epidural and regional blocks], is currently recognized as best practice in pain management [17–20]. Non-specific NSAIDs are considered part of postoperative pain management, resulting in improved clinical and economic outcomes, but their role has been limited in the peri- and postoperative setting due to (i) platelet dysfunction, (ii) renal problems, (iii) gastrointestinal toxicity and (iv) bleeding complications resulting from (i) and/or (iii) [21].

This article provides an overview of the burden, outcomes, economic impact and pharmacological management of acute postoperative pain with a focus on the role of NSAIDs and the use of cyclooxygenase-2 (COX-2)-specific inhibitors as highly effective adjunctive analgesic agents and a key component of a multimodal analgesic regimen.

**Epidemiology of acute postoperative pain**

It has been estimated that, in established market economies, 5–10% of the population undergo surgery each year [22]. In the USA alone, based on hospital discharge data for the year 2000, approximately 40 million inpatient procedures were performed [23], and it is likely that outpatient procedures exceeded this number.

Patients have a high degree of preoperative anxiety regarding pain. According to a national telephone survey, 57% of adults reported that postoperative pain is their primary preoperative concern [24]. A recent study of 544 patients undergoing a variety of surgical procedures reported that, while 89% of patients expected to have moderate to severe postsurgical pain, only 36% believed that medication would adequately control this pain [25].

These expectations are not surprising considering that other studies have reported that up to 75% of patients have moderate to severe postoperative pain, which often results from inadequate administration of analgesic medication [22]. Postsurgical pain is not limited to the immediate postoperative recovery, but has been reported in 76% of patients after 1 week and in 19% of patients after 3 months, 27% and 3% of patients reporting moderate to severe pain at these two time points, respectively [25]. One common reason for the high incidence and duration of pain may be that critically ill patients often have particular difficulty expressing pain due to the presence of physical or mental factors that impede effective communication. These factors include altered mental status and the use of endotracheal tubes/mechanical ventilation, sedatives and neuromuscular blockers [26, 27]. In one study, 63% of intensive care unit (ICU) patients reported moderate to severe pain [28], yet according to another study, ICU patients receive only 30–37% of the maximum dose of opioid ordered by the physician [29].

**Physiological response to pain**

Although the pathophysiology of pain is beyond the scope of this review, it is important to note the physiological response to pain, as this can have significant impact on outcomes.

During surgery, general anaesthesia is used to inhibit cortical responses to tissue injury, and neuromuscular blocking agents prevent muscle spasms. However, sympathetic, neuroendocrine and biochemical responses to the surgical insult are generally uncontrolled [30]. The stress response to surgery affects many body systems and peaks during the postoperative period [31]. These physiological responses include decreased chest wall compliance, decreased tone of the gastrointestinal and urinary tracts, and increases in cardiac output and blood pressure, cardiac workload, metabolism and oxygen consumption. In addition, there are marked increases in catabolic hormones, such as catecholamines, adrenocorticotropic hormone, antiuretic hormone, glucagons and aldosterone, while there are concurrent decreases in anabolic hormones, such as insulin and testosterone. These endocrine effects ultimately increase plasma glucose/hyperglycaemia and plasma cyclic AMP, free fatty acid, ketone and blood lactate levels, as well as increasing general metabolism and oxygen consumption. The purpose of these normal responses to trauma/surgery is to mobilize stored substrates and ultimately produce the catabolic state required for healing of the damaged tissue.

Uncontrolled pain exacerbates this normal stress response, which may result in serious complications,
particularly for high-risk patients, such as those with pre-existing pulmonary or cardiac disease. Severe pain also causes reflex muscle spasm, intensifying pain especially in joint and spine surgery [30].

While acute pain is temporally and temporarily related to a precipitating event and thus has a defined aetiology, pain is considered to be chronic if it is unlikely to resolve or if it lasts for a period of 3 months after a precipitating event [15, 32]. Chronic pain generally arises as a result of neuronal plasticity following protracted central nervous system hyperexcitability [7, 33, 34], and it has been suggested that appropriate analgesic therapy, such as pre-emptive analgesia, prevents the establishment of central sensitization [35].

Consequently, these physiological responses have significant implications for postoperative outcomes, especially if pain is inadequately treated, thereby maintaining the pain state and leading to enhanced central nervous system sensitization. In the case of postoperative pain, a chronic pain state may be considered after pain of 2 months’ duration [36].

**Acute postoperative pain and outcomes**

**Clinical outcomes**

As previously mentioned, the majority of acute pain patients, despite the availability of effective analgesics, remain in moderate to severe pain. Unrelied pain is not only a quality-of-life (QOL) issue but results in immune, genetic and neural changes that can progress to a chronic pain syndrome if not adequately addressed [30, 33]. Additionally, the prognosis may be compromised, since patients with severe pain have higher postoperative morbidity and mortality rates [31].

The negative clinical outcomes arising from undertreatment of acute postoperative pain are summarized in Table 1 [13, 18, 19, 30, 31, 37, 38]. These outcomes result in the extended hospitalization, higher health-care costs and reduced patient satisfaction that ultimately contribute to the significant economic and QOL burden associated with undertreated pain [19]. In addition, poorly treated acute pain may exacerbate the underlying pathophysiology of many illnesses and injuries. Prevention and effective relief of acute pain may reduce complications and their consequences, thereby favourably affecting both economic and patient outcomes.

There is clear evidence that more aggressive management of postoperative pain can improve outcomes, but these approaches are not totally risk-free. While some of the risks associated with specific analgesic agents will be discussed in the section on pharmacological therapy, there are other risks associated with the techniques that have customarily been used in drug administration. These risks include infusion pump failure, line infections and errors in drug administration.

Although iatrogenic complications are a concern, new pain management techniques are safe when well managed, especially if integrated into a multimodal approach, and their benefits outweigh their risks [8, 22, 31]. Evidence suggests that PCA and particularly epidural anaesthesia/analgies are useful techniques, the latter demonstrating marked reductions in morbidity outcomes in patients undergoing major abdominal and orthopaedic procedures (Table 2) [39–42].

**Economic outcomes**

Although the economic burden of pain is significant, it is difficult to estimate given the variety of diagnoses in which pain may be present. The American Psychological Association reports that the burden of pain in the USA, both acute and chronic, was US$90 billion in the year 2000 [43]. This value included direct costs resulting from medical resource utilization as well as indirect costs relating to lost productivity.

Pinpointing the total annual cost of acute postoperative pain is even more difficult, because pain is experi-

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**Table 1. Clinical outcomes of postoperative pain. [13, 18, 19, 30, 31, 37, 38]**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tr>
<td>Pulmonary</td>
<td>Chest and abdominal muscle splinting results in reduced tidal volume, vital capacity and ventilation. Inhibition of coughing and inability to mobilize secretions contributes to atelectasis and pulmonary infection.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Sympathetic nervous stimulation results in tachycardia and hypertension. Increased cardiac workload and myocardial oxygen demand may result in perioperative myocardial ischaemia or infarct and cardiac failure.</td>
</tr>
<tr>
<td>Endocrine and metabolic</td>
<td>Catabolic hormonal response becomes exaggerated, resulting in sodium and water retention from increased anti-diuretic hormone and aldosterone secretion, as well as hyperglycaemia from increased cortisol and adrenaline secretions.</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>Restricted mobility contributes to development of serious thromboembolic events, such as deep vein thrombosis and pulmonary embolism. Cortisol and catecholamine secretion in response to pain and anxiety increase blood viscosity and clotting, fibrinolysis and platelet aggregation.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased autonomic nervous activity affects intestinal smooth muscle and sphincter activity, slowing motility of the gut. Gastric distension and intestinal dilatation with postoperative ileus may also occur. Opiates prolong postoperative ileus.</td>
</tr>
<tr>
<td>Urological</td>
<td>Autonomic nervous system imbalance of smooth muscle may contribute to postoperative urinary retention. Opiates may contribute to urological dysfunction.</td>
</tr>
<tr>
<td>Immunological</td>
<td>Pain alters immune system activity, resulting in infection-related complications in high-risk surgical patients.</td>
</tr>
<tr>
<td>Central nervous system/psychological</td>
<td>Up-regulation via peripheral and central sensitization may result in development of chronic pain syndromes following surgery. Unrelied pain causes sleep deprivation, anxiety, helplessness and fatigue.</td>
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encared during nearly every procedure, and separating the added cost of pain from the cost of the surgery also presents challenges. While trying to itemize actual costs may be difficult, several factors have been identified that are drivers of either direct or indirect costs.

Direct costs. Direct medical costs are the costs of all health-care resources used for a treatment, procedure or intervention, and consist of resources used for both the intervention itself and the treatment of any side-effects relating to the intervention. The primary direct-cost categories for postoperative pain include analgesics, devices, nursing time and daily charges for time spent in the postanaesthesia care unit (PACU) or ICU [8, 44]. Consequently, the main driver of direct costs is the length of hospital stay (LOS), and therefore the development of any complications associated with the surgery or with the postoperative analgesic regimen can lengthen LOS and increase costs.

Optimizing postoperative pain management accelerates patient recovery and expedites hospital discharge, thereby reducing LOS and associated hospital costs [8, 44]. Even in ambulatory surgery, pain severity is associated with recovery and discharge rate, higher pain scores being predictive of increased recovery time [45].

The most economical approach to pain management is the use of the least expensive, least invasive, yet most effective treatment. However, in postoperative pain, medical and economic outcomes in both the short and long term are often directly related to appropriate pain management. There has been an association between type of treatment and the incidence of postoperative complications such as myocardial ischaemia, pulmonary dysfunction and development of pneumonia, or thromboembolic events that result from decreased mobility [38, 39, 46, 47]. These complications can significantly increase direct costs by extending LOS, and a reduction in complications is clearly desirable, not only from an economic point of view but also from the perspective of patient safety [48].

Additionally, patients who continue to have pain after discharge or develop chronic pain contribute to the economic burden resulting from costs for health-care resource utilization in the form of physician visits, pain medications and other analgesic therapies [49]. Approximately 22.5% of patients visiting a chronic pain clinic have reported surgery as an antecedent cause of their chronic pain [50].

Indirect costs. Indirect costs are related to lost productivity and the cost of time spent caring for patients by their families or a caregiver. These costs have not been evaluated for patients with acute postoperative pain. However, extended recovery periods due to pain or complications are likely to increase the losses for productivity and lost work time for the patient. Negative clinical outcomes of poor acute postoperative pain management, such as the development of chronic pain syndromes, may additionally affect indirect costs. Work loss is a key indirect cost for patients experiencing chronic pain following surgery, though a direct link with the postoperative pain management strategy has not been shown [51, 52].

Costs related to time spent caring for a patient by a patient’s family or a caregiver also contribute to overall costs and are likely to increase as ambulatory surgery becomes the norm for a variety of interventions [48]. Time spent managing adverse events of medication will also increase the indirect costs for patients undergoing ambulatory surgery. However, ambulatory surgery also means quicker patient mobility, which may expedite recovery, and the reduced direct costs resulting from quick recovery and short LOS may ultimately offset short-term indirect costs. Consequently, patient and family education will become essential components of managing postoperative pain at home.

Economic impact of pain management strategies. Pain management has evolved from intermittent, intramuscular, opioid injections to PCA and the use of a multimodal approach that combines drugs and techniques. With these advances in pain management, reductions in recovery time and LOS are likely to justify the newer, more expensive techniques and the maintenance of a hospital-based acute pain service. Reviews of the evidence suggest that PCA in comparison with conventional treatment results in a 22–38% reduction in LOS for cholecystectomies, thoracotomies and lumbar laminectomies, with associated savings of US$984–1735 per patient [8, 44]. Similarly, reductions in LOS have been observed with the use of PCA in radical prostatectomy, major vascular surgery, cancer surgery and nephrectomy [47].

Pain management using epidural analgesia not only reduces overall LOS but also significantly reduces ventilator time, ICU–LOS and gut function recovery time, a key indicator of recovery and a discharge criterion [8, 40, 41, 44].

A few studies have documented the economic impact of non-specific NSAIDs as an alternative or adjunct to opioids in the management of postoperative pain. Burke et al. [53] studied the cost consequences (i.e. clinical and economic outcomes) of ketorolac in postoperative pain management compared with patients who did not receive non-specific NSAIDs. They reported that ketorolac resulted in significant cost savings, resulting mainly from a 4-fold reduction in narcotic-related adverse drug events and reduced LOS [53]. Similar decreases in health-care resource utilization associated with ketorolac compared with opiates were observed in a study that also showed

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**Table 2. Improved clinical outcomes reported with use of epidural and spinal analgesic techniques in orthopaedic and abdominal surgery [39–42]**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reduction</th>
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<tr>
<td>Postoperative ileus</td>
<td>2–4 days</td>
</tr>
<tr>
<td>Intraoperative blood loss</td>
<td>30%</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>40%</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
<td>50%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>78%</td>
</tr>
<tr>
<td>Myocardial ischaemia</td>
<td>70%</td>
</tr>
<tr>
<td>Mortality</td>
<td>25%</td>
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decreased overall patient costs despite the higher acquisition costs of ketorolac [54]. In both of these studies, LOS was the main cost driver.

Timing of drug use is another important parameter. Pavlin et al. [45] recently reported that three key factors affecting patient and economic outcomes—postoperative pain, opioid-related side-effects and time to discharge—were reduced when non-specific NSAIDs or local anaesthetics were used intraoperatively to prevent pain before patient awakening.

**QOL outcomes**

Pain is an important predictor of QOL that affects other QOL domains, such as physical function, social function, personal independence and psychological state [55]. The overall effect is a decreased QOL that affects subjective areas, such as depression, anxiety and patient satisfaction. Consequently, pain sufferers are more likely to have an anxiety or depressive disorder [1].

The management of acute postoperative pain probably plays a role in QOL in both the short and the long term, but this has been little studied. QOL evaluation in the immediate postoperative period has tended to focus on functional status and pain dimensions, but some generic QOL instruments have been shown to be of value in a pain-specific setting. The Short Form 36 (SF-36) has been the most well-studied generic QOL instrument and is responsive in a variety of surgical procedures [56–58].

It is known that successful postoperative pain management should enable a recovering patient to be more physically active and more mentally alert and should enable earlier re-initiation of oral feeding in certain types of surgery [18]. Less successful pain management and the side-effects of analgesics used to treat pain can diminish patients' QOL, particularly if pain and/or side-effects of medication occur for prolonged periods [18].

In treating postoperative pain, the most immediate QOL issues pertain to a trade-off between pain and nausea. These two symptoms are the most common reasons for readmission or delayed discharge following surgery [59]. Pain is traditionally treated with opiates, resulting in nausea and vomiting in 20–50% of patients [60]. Patients generally have a preference for pain if it means less nausea and vomiting. Eberhart et al. [61] surveyed 220 patients preoperatively and found that the patient concerns having the largest impact in the immediate postoperative period (as a percentage of the preference decision) were postoperative nausea/vomiting (49%), pain (27%), alertness (13%) and additional costs (11%).

In another survey, by Macario et al. [62], patients ranked a series of postoperative outcomes from the most undesirable to least undesirable (Fig. 1). Pain was ranked number 3, while vomiting, an outcome that is a common side-effect of anaesthetic/analgesic treatment, was ranked as the least desirable. These results were similar to a previous study that also determined that both pain and nausea/vomiting were key concerns of patients undergoing surgery [63]. Consequently, preoperative planning between the physician and patient can help improve postoperative care by considering specific patient preferences.

In a more direct correlation between adequate pain management and immediate postoperative QOL, a study by Carli et al. [64] in colorectal surgery patients compared postoperative outcomes between morphine-based PCA and a multimodal approach using bupivacaine/fentanyl via the epidural route. Not only did the multimodal approach provide increased pain relief and lower fatigue, but it also resulted in significantly superior health-related QOL (measured by the SF-36) at the 3- and 6-week time points and accelerated clinical outcomes associated with discharge, such as mobility and normal feeding. Importantly, the mental component score on the SF-36 had returned to baseline by 3 weeks in the multimodal group but did not reach baseline values by 6 weeks in the PCA–morphine group.

Long-term QOL can also be affected, especially if chronic pain syndromes develop as a result of inadequate postoperative pain management. A study evaluating the long-term impact of pain in transplant patients found that after 6–24 months 53% of patients reported chronic pain that affected physical function, vitality and general health [57]. Patients with pain also scored worse in areas of depression than patients without pain. Similar results

![Fig. 1. Ranking of most undesirable to least undesirable postoperative outcomes. Percentages indicate proportion of patients ranking a specific outcome as the most undesirable. Data from Macario et al. [62].](https://academic.oup.com/rheumatology/article/42/suppl_3/iii40/1788133)
were reported for both acute (1 week) and chronic (3 month) postoperative pain in patients undergoing a variety of inpatient and outpatient surgical procedures [65, 66]. At both time points, the presence of pain had significant negative effects on QOL, resulting in reductions in the activities of daily living and increased depression independently of other personal or psychological characteristics.

Effective postoperative pain management has also been shown to reduce the risk of depression following coronary artery bypass surgery (CABG) [67]. Eighty patients undergoing CABG were randomized to either high-dose thoracic epidural analgesia (most effective analgesia) or intravenous morphine PCA. Patients receiving the high-dose regimen reported significantly less pain, depression and post-traumatic stress using standard psychological assessment tools.

Although a more recent study evaluating short- and long-term (6 months) postoperative pain in thoracotomy patients did not specifically evaluate QOL, the implications for QOL outcomes are clear [68]. In this study, postoperative PCA–morphine was compared with a multimodal regimen (epidural bupivacaine/morphine) initiated either before or after operation. The presence of immediate postoperative pain with inadequate postoperative pain relief was associated with development of chronic pain; 83% of patients with pain on the second postoperative day went on to develop chronic pain. The group receiving multimodal analgesia that was initiated pre-emptively had the most favourable outcomes and was significantly superior to the other two groups in both incidence and intensity of pain at 6 months.

An earlier study found similar results, with a lower incidence of chronic pain at the 3- and 6-month follow-up in patients receiving continuous epidural block for thoracic surgery started pre-emptively before surgery compared with postsurgical analgesia [69]. Furthermore, a systematic review of chronic pain following surgery found that the level of postoperative pain is a significant predictor of chronic pain in breast, thoracic and hernia surgery [6].

Pharmacological treatment of acute postoperative pain

Multimodal analgesia in which several drugs and techniques are combined is increasingly recognized as the most effective approach to postoperative pain, especially if used pre-emptively (before tissue injury) and continued postoperatively. With this strategy, pain impulses can be blocked in different locations by different drugs: non-specific NSAIDs to mediate peripheral inflammation, local anaesthetics (e.g. bupivacaine) to block afferent nerve activity, and opioids (e.g. morphine, fentanyl) to modulate central pain processes [18, 70, 71]. However, the value of multimodal analgesia may be restricted by several factors, including lack of an in-hospital acute pain service [72], as well as by the limitations of individual agents used in the regimen.

Opioids

Morphine and its derivatives are the foundation of analgesic therapy in patients with moderate to severe pain [13]. Opiates block pain transmission in the central nervous system by binding specific opiate receptors on nerves. The most commonly used intravenous opioids include morphine, meperidine and fentanyl.

Administration of opioids has evolved from intermittent injections to a PCA technique that may be used to deliver intravenous, epidural or spinal anaesthesia/analgesia. Less severe pain can be treated effectively with oral opioids such as codeine, hydrocodone and oxycodone, used alone or in combination with paracetamol (acetaminophen) or non-specific NSAIDs. Additionally, transdermal administration systems are a recent advancement that are most often used with fentanyl.

Opioids are generally effective in reducing pain, although 26–75% of patients still complain of insufficient analgesia [30]. Despite their efficacy, opioids have been underused, often because of fear of dependency [73]. When they are used, their efficacy may be limited by incorrect dosing, suboptimal route of administration, inadequate frequency, poor opioid selection and the inappropriate use of adjunctive agents.

Opioid efficacy is also limited by adverse events that affect the central nervous system and the gastrointestinal tract. In addition to nausea, vomiting, pruritus, urinary retention and hypotension, the occurrence of respiratory depression may be of particular significance [17, 60, 74, 75]. This event, which occurs in <1% of patients receiving opioids, can nevertheless pose a serious problem following thoracic surgery, as many patients have compromised pulmonary function before surgery [38]. A 10-yr retrospective study of 60 722 surgical patients receiving opioid medication found that 2.7% experienced opioid-related adverse events [75]. Compared with matched controls, patients experiencing opioid adverse events had significantly extended hospital lengths of stay (0.53 more days) and increased costs (US$840 higher per hospital admission).

For all the above reasons, effective alternatives to opioids are desirable, as are adjunctive agents that can be used to limit the opioid dose.

Tramadol

Tramadol is considered a non-narcotic analgesic. However, it is centrally acting with a weak, non-selective affinity for most opioid receptors, but with a high affinity for the mu-receptor [76]. Other mechanisms contributing to its analgesic properties include inhibition of neuronal uptake of noradrenaline (norepinephrine) and serotonin [76]. Compared with other non-narcotic analgesics in the postoperative setting, its efficacy is better than that of paracetamol and similar to or better than those of the non-specific NSAIDs diclofenac and ketorolac [77–80].

Although it has a lower risk of dependency and respiratory depression, its side-effect profile is similar
to that of opioids, with a high incidence of nausea (24–40%), vomiting (9–17%), constipation (24–46%) and dizziness (26–33%) [76, 78].

**Paracetamol**

Simple analgesics such as paracetamol are not drugs of choice for postoperative pain, unless the pain is mild, although they are commonly used in combination with opioids (e.g. codeine, oxycodone). In comparison with non-specific NSAIDs, paracetamol’s analgesic potency is lower, but it is synergistic when used in combination with opioids and provides an opioid-sparing effect [70, 81, 82]. Thus when non-specific NSAIDs are contraindicated, paracetamol may be used. Limitations of paracetamol include liver and renal toxicities, and a recent study also implicates paracetamol in gastrointestinal toxicity [83].

**Non-specific NSAIDs**

Unless contraindicated, non-specific NSAIDs have been considered the drugs of choice for the management of mild to moderate postoperative pain [13]. Their mechanism of action is via inhibition of COX, and non-specific NSAIDs block both the constitutive COX-1 isoform, responsible for gastric protection and platelet function, and the inducible proinflammatory isoform, COX-2 [84, 85]. Thus, non-specific inhibition results in both the desired analgesic effects and unwanted side-effects.

Analgesic efficacy is obtained at the level of tissue injury by inhibiting local mediators of pain and inflammation and preventing peripheral sensitization, as well as centrally, by inhibiting COX in the spinal cord, thereby reducing neuronal input from peripheral inflammation during the postoperative period [35, 86–88].

Non-specific NSAIDs provide excellent pain relief and, when used in combination with opioids for more severe pain, may result in an opioid-sparing effect [31], thus reducing opioid-related side-effects, such as sedation, nausea, vomiting, ileus and urinary retention. Some studies have not shown a clear benefit of adjunctive NSAID use, but these were generally pre-emptive studies in which the NSAID was given preoperatively without continuation into the postoperative period [89–92]. Multimodal regimens are more likely to be effective when initiated pre-emptively and continued during the postoperative period [68, 93].

Advantages of non-specific NSAIDs include lack of sedation and respiratory depression, a low abuse potential, and no interference with bowel or bladder function [31]. However, the major side-effects that limit their perioperative use are related to their inhibition of the COX-1 enzyme, and include renal toxicity, platelet dysfunction with haemorrhage, and gastrointestinal toxicity, including serious complications, such as gastrointestinal ulceration and bleeding [21, 85, 94, 95].

Since renal synthesis of the vasodilatory prostaglandin prostacyclin is under the control of both COX-1 and COX-2, reduction in renal function may occur with both non-specific NSAIDs and COX-2-specific inhibitors, leading to reduced renal blood flow and filtration and resulting in fluid and sodium retention [96]. Additionally, available evidence suggests that differences in renal effects may exist even among the COX-2-specific inhibitors [96, 97]. From the perspective of renal function, both non-specific NSAIDs and COX-2-specific inhibitors are usually safe in healthy patients [98], but these drugs should be used cautiously in patients at risk of renal problems (i.e. the elderly and those with pre-existing renal dysfunction).

Inhibition of COX-1 by non-specific NSAIDs also reduces platelet aggregation by blocking the formation of thromboxane A₂, and inhibition of COX-2 blocks production of prostaglandin I₂ (prostacyclin), which normally inhibits platelet aggregation. The net result of these opposing effects of non-specific NSAIDs is not fully understood [95], but the known platelet effects of non-specific NSAIDs may be a source of concern for the perioperative use of these agents in some types of surgery. There are as yet insufficient data to determine the exact source of the higher cardiovascular events that have been observed with the use of rofecoxib [99], but the possibility of unopposed platelet aggregation as a factor in such events may be a source of concern when using COX-2-specific agents [100]. Consequently, as with renal function and if not directly contraindicated, non-specific NSAIDs and COX-2-specific inhibitors should be used with care in patients with risk factors for platelet dysfunction (increased age, pre-existing coagulation deficiencies or thromboembolic conditions, and patients undergoing major gynaecological and cardiac surgery).

The most well-known complications of non-specific NSAIDs are their gastrointestinal side-effects. Prostaglandins protect the gastrointestinal mucosa by limiting acid damage and facilitating bicarbonate release, mucus secretion and adequate blood flow. Non-specific NSAIDs can cause gastric damage by topical and/or systemic mechanisms regardless of the route of administration, which can result in ulceration, perforation and life-threatening gastrointestinal bleeding [101, 102]. Gastroprotective agents such as H₂-receptor antagonists (ranitidine, cimetidine), proton pump inhibitors (omeprazole) and prostaglandin analogues (misoprostol) are often used but can significantly increase treatment costs [103, 104]. These drugs have variable efficacy in preventing serious outcomes [105, 106] and may be of limited value in the postoperative setting. Risk factors for gastrointestinal side-effects include increasing age, prior gastrointestinal history, anticoagulation therapy and comorbid disease [107].

The limited availability of parenteral formulations of non-specific NSAIDs may have also restricted their perioperative use. Ketorolac is currently the only parenteral NSAID approved in the USA; consequently, it is the drug with which other new analgesics are compared. It is used extensively despite its significant side-effect profile, although specific guidelines have been developed regarding dosage and the use of parenteral ketorolac to try to ameliorate risks [108, 109].
Role of COX-2-specific inhibitors in postoperative pain

Specific inhibitors of COX-2 were developed to provide safer alternatives to non-specific NSAIDs without compromising efficacy. These COX-2-specific inhibitors specifically target the proinflammatory isoform (COX-2) while sparing COX-1. This specificity accounts for their safer gastrointestinal profile relative to non-specific NSAIDs [85], and they have demonstrated efficacy and tolerability for painful inflammatory conditions such as osteoarthritis and rheumatoid arthritis. The observed gastrointestinal safety and tolerability, lack of platelet effects and analgesic properties of these drugs suggested their use as a means of addressing some of the limitations of currently used postoperative analgesics.

The oral COX-2-specific inhibitors currently approved in the USA (celecoxib, rofecoxib and valdecoxib) and in various countries in Europe (celecoxib, rofecoxib, valdecoxib and etoricoxib) all have demonstrated efficacy in trials of postoperative pain. Additionally, parecoxib, which has been approved in the UK and several other European countries, has also been shown to be effective. Parecoxib has been developed as a parenteral formulation (both intramuscular and intravenous) and, as the prodrug of valdecoxib, can potentially facilitate a parenteral-to-oral switch.

Most of the studies evaluating the analgesic efficacy of these drugs used the dental pain model [110–119], currently considered the standard for evaluating drugs for analgesic efficacy in acute pain [120]. The dental pain studies generally characterized COX-2-specific inhibitors as having favourable tolerability and analgesic efficacy as a result of their pharmacokinetic advantages of rapid onset (12–13 min in the case of parecoxib, 20–60 min for the other drugs) and long duration of action (6–24 h depending on drug and dose). In particular, parenteral parecoxib administered before or after operation and preoperative oral valdecoxib have been shown to be superior to placebo in the oral surgery model [114, 115, 117, 121]. The former also demonstrated efficacy similar to that of ketorolac [115], and the latter showed superior efficacy to rofecoxib with respect to onset and duration of analgesia, as well as differences in pain intensity and pain relief (Fig. 2) [117].

Several studies have evaluated COX-2-specific inhibitors in a variety of inpatient and outpatient procedures, including gynaecological surgery [122, 123], orthopaedic surgery [124–130], radical prostatectomy [131] and otolaryngological surgery [132–134]. While these studies are heterogeneous with regard to evaluated outcomes as well as to the drugs and protocols used, they nearly all provide an indication of efficacy and showed an opioid-sparing effect that ranged from 20% to 70%. The one notable exception is the study on prostatectomy, which found no benefit of rofecoxib either for pain relief or reduction in opioid consumption [131]. It has been suggested that the efficacy of non-specific NSAIDs for postoperative pain depends on the type of surgery [21], and this study suggests the same may be true for COX-2-specific inhibitors. However, it should be noted that this study used a single oral dose of rofecoxib 1 h before surgery, rather than continuing pre-emptive analgesia into the postoperative period.

In the few direct comparisons with other analgesics, parecoxib was found to be as effective as intravenous parecoxib, but it had a superior gastrointestinal profile and a similar analgesic efficacy. Valdecoxib was also found to be as effective as rofecoxib and parecoxib in terms of analgesic efficacy, but it had a better gastrointestinal profile. The observed gastrointestinal safety and tolerability, lack of platelet effects and analgesic properties of these drugs suggested their use as a means of addressing some of the limitations of currently used postoperative analgesics.

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Fig. 2. Analgesic efficacy of oral valdecoxib 40 mg compared with placebo and rofecoxib 50 mg in patients undergoing oral surgery. (A) Mean pain intensity differences (± standard error). (B) Mean pain relief (± standard error). Valdecoxib was significantly different from placebo at all time points after 30 min and significantly different from rofecoxib at all time points after 45 min for both pain intensity and pain relief (P < 0.05). Figure reprinted with permission from Fricke et al. [117].
ketorolac and superior to intravenous morphine 4 mg following gynaecological surgery [122]; pre-emptive rofecoxib was demonstrated to be superior to paracetamol for postoperative pain after otolaryngological surgery [134]; and celecoxib was at least as effective as paracetamol/hydrocodone following orthopaedic surgery [126].

Most of the studies have focused on efficacy and have provided little information on clinical, economic or patient-centred outcomes.

While published studies have reported a reduction in opioid consumption with the use of COX-2-specific inhibitors, the incidence of adverse events generally associated with opioids, such as nausea and vomiting, does not seem to be significantly reduced with the use of these agents. Other clinically important outcomes affecting recovery and prognosis have rarely been reported, suggesting a need for further studies.

Of special importance is the effect of COX-2-specific inhibitors on bleeding. It may be expected that these drugs will not have a significant effect on bleeding because of the lack of platelet effects [135, 136], and none of the studies have reported clinically significant bleeds. However, case reports have suggested a potential interaction with warfarin and an elevation in the international normalized ratio that may occur as much as several months after initiating therapy with COX-2-specific inhibitors [137].

Only two studies reported outcomes of economic importance. Bekker et al. [125] determined that there was no significant difference in PACU stay or LOS between groups of patients pre-emptively treated with rofecoxib or placebo, despite a 36% reduction in morphine requirement in the rofecoxib group. Consistent results were obtained in a study by Issioui et al. [134], in which there were no significant differences in time spent in the PACU or day surgery unit among groups of patients pre-emptively treated with rofecoxib. However, these authors found that the significantly superior efficacy of rofecoxib resulted in high patient satisfaction that could be obtained at modest incremental cost compared with the use of no drug or paracetamol.

A similar dearth of information is available on QOL outcomes. While several studies have rated medication or treatment as good to excellent, only a single study used an instrument that evaluates domains associated with QOL. Gimbel et al. [126] used the American Pain Society Patient Outcomes Questionnaire, which includes several measures of QOL, to evaluate outcomes after 5 days of postoperative pain treatment with celecoxib or hydrocodone/paracetamol. For all outcomes on the questionnaire, celecoxib demonstrated significantly superior QOL (Fig. 3).

Although the available data suggest that COX-2-specific inhibitors may provide a useful alternative or adjunct to the currently used analgesics, it is evident that more research is needed to clearly establish the benefits and value that can be obtained with these agents.

### Conclusions

The inadequate treatment of postoperative pain is a common problem that affects a variety of outcomes and has implications at all levels of health-care. The solution to the problem is complicated by the availability of less than optimal management strategies. A multimodal approach has been suggested to provide the best efficacy but is limited by the side-effects of the drugs often used in pain management. The efficacy and safety of the COX-2 inhibitors suggest that these drugs may provide an alternative or adjunct to currently used analgesic regimens. Despite the number of papers that have

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**Fig. 3. Scores on the American Pain Society Patient Outcomes Questionnaire in patients treated for postoperative pain after orthopaedic surgery with celecoxib or hydrocodone/paracetamol.**

* \( P < 0.013 \) vs hydrocodone/paracetamol. Reprinted with permission from Gimbel et al. [126].

![Diagram showing scores on the American Pain Society measure](https://academic.oup.com/rheumatology/article-fig/3/suppl/iii48/1788133)
recently been published on the use of COX-2-specific inhibitors for postoperative pain, this approach to pain management is in the developmental stage. There are still significant gaps in our knowledge not only of their specific analgesic mechanisms but also, more importantly, of how the proposed actions of these drugs will translate into clinically relevant and measurable outcomes of effectiveness and safety that can be of value in lessening the burden of postoperative pain. Further research that specifically compares different protocols and drugs can help optimize efficacy. Additionally, such studies need to incorporate endpoints to evaluate clinical, economic and patient-centred outcomes in addition to those of efficacy and general safety. Nevertheless, COX-2-specific inhibitors represent a group of agents that show promise in reducing the burden of postoperative pain.

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References

Burden of postoperative pain


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