

# Poorly controlled postoperative pain: prevalence, consequences, and prevention

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**Abstract:** This review provides an overview of the clinical issue of poorly controlled postoperative pain and therapeutic approaches that may help to address this common unresolved health-care challenge. Postoperative pain is not adequately managed in greater than 80% of patients in the US, although rates vary depending on such factors as type of surgery performed, analgesic/anesthetic intervention used, and time elapsed after surgery. Poorly controlled acute postoperative pain is associated with increased morbidity, functional and quality-of-life impairment, delayed recovery time, prolonged duration of opioid use, and higher health-care costs. In addition, the presence and intensity of acute pain during or after surgery is predictive of the development of chronic pain. More effective analgesic/anesthetic measures in the perioperative period are needed to prevent the progression to persistent pain. Although clinical findings are inconsistent, some studies of local anesthetics and nonopioid analgesics have suggested potential benefits as preventive interventions. Conventional opioids remain the standard of care for the management of acute postoperative pain; however, the risk of opioid-related adverse events can limit optimal dosing for analgesia, leading to poorly controlled acute postoperative pain. Several new opioids have been developed that modulate  $\mu$ -receptor activity by selectively engaging intracellular pathways associated with analgesia and not those associated with adverse events, creating a wider therapeutic window than unselective conventional opioids. In clinical studies, oliceridine (TRV130), a novel  $\mu$ -receptor G-protein pathway-selective modulator, produced rapid postoperative analgesia with reduced prevalence of adverse events versus morphine.

**Keywords:** acute pain, chronic pain, surgical procedures, analgesics, opioid

## Introduction

Surgery and anesthesia are critical health-care services that reduce the risk of death and disability among millions worldwide each year, and the need for these services is expected to continue to increase over the next decade.<sup>1</sup> Globally, nearly 313 million operations were performed in 2012,<sup>2</sup> whereas in the US an estimated 28 million inpatient surgical procedures and 48 million ambulatory surgeries were reported in 2006 and 2010, respectively.<sup>3,4</sup> Although possibly life-saving, surgery is also associated with potential harm, which frequently includes pain during and after the procedure. Despite improved understanding of pain mechanisms, increased awareness of the prevalence of postsurgical pain, advances in pain-management approaches, and other focused initiatives aimed at improving pain-related outcomes in recent decades, inadequately controlled postoperative pain continues to be a widespread, unresolved health-care problem.

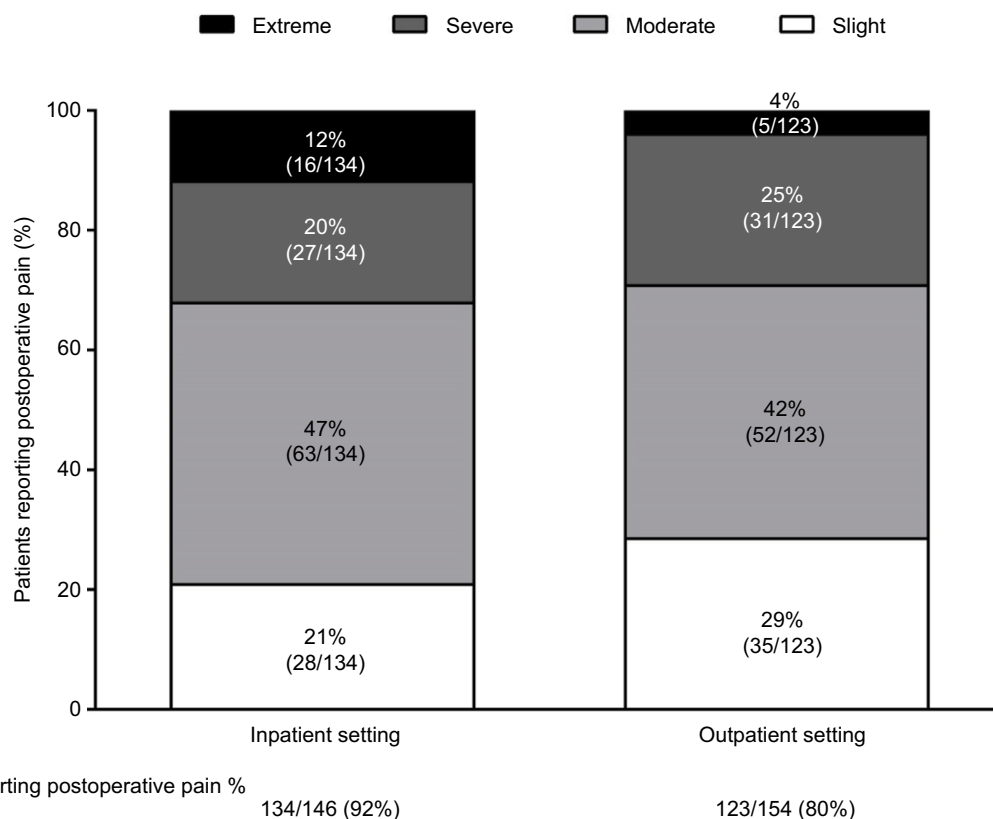
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Suboptimal acute-pain management in surgery patients is accompanied by an array of negative consequences, including increased morbidity, impaired physical function and quality of life, slowed recovery, prolonged opioid use during and after hospitalization, and increased cost of care. In addition, early postoperative pain appears to trigger persistent pain that may last for months after surgery in a substantial proportion of patients. To prevent the progression from acute to chronic postoperative pain, more aggressive analgesic/anesthetic measures are needed to reduce the incidence and intensity of acute pain during and immediately after surgery. Although research on preventive interventions is limited, some promising results have been reported in studies of local anesthetics and nonopioid analgesics.<sup>5-7</sup> In addition, a new class of opioid analgesics – selective agonists at the  $\mu$ -opioid receptor – with a potentially expanded therapeutic window compared with conventional, unselective opioid therapies is currently in development.<sup>8-10</sup> In early-phase studies, the  $\mu$ -receptor G-protein pathway-selective modulator oliceridine produced comparable but more rapid pain relief than morphine and fewer opioid-related adverse events (AEs), suggesting potential benefits in the prevention of postsurgical pain.<sup>10,11</sup>

In this review, we examine the prevalence of poorly controlled acute postoperative pain and the major factors that may predict its occurrence. In addition, the consequences of inadequate pain management after surgery are described, with an emphasis on the potential development of chronic pain. Finally, we present findings from clinical studies of treatment approaches that may control acute postoperative pain more effectively, prevent its negative effects on patients' health, function, and quality of life, and reduce the risk of progression to persistent pain.

## Rates and risk factors of inadequately controlled acute postoperative pain

According to the US Institute of Medicine, 80% of patients who undergo surgery report postoperative pain, with 88% of these patients reporting moderate, severe, or extreme pain levels.<sup>12</sup> In a national US survey of 300 adults who had undergone surgery within the previous 5 years, 86% of patients experienced postsurgical pain overall, and 75% of those who reported pain described its severity as moderate–extreme during the immediate postoperative period (Figure 1).<sup>13</sup>



**Figure 1** Proportion of patients with postoperative pain in inpatient and outpatient settings by pain severity.

**Note:** Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. *Current Medical Research and Opinion*. Jan 2014. Reprinted by permission of the publisher (Taylor & Francis Ltd, <http://www.tandfonline.com>).<sup>13</sup>

Acute pain has been commonly reported across many different surgery types, including both hard- and soft-tissue surgeries, despite administration of analgesic medication after surgery.<sup>13–19</sup> Evidence from a prospective German cohort study of 50,523 patients from 179 surgical groups showed that pain scores on the first postoperative day were highest after obstetric and orthopedic/traumatic procedures, but scores were high after even common minor surgical procedures, such as appendectomy, cholecystectomy, hemorrhoidectomy, tonsillectomy, and some laparoscopic procedures.<sup>19</sup> In a systematic literature review in which pain scores were pooled from 165 studies of acute pain following major surgery (abdominal, thoracic, orthopedic, and gynecological), in the first 24 hours after surgery, mean incidence of moderate–severe pain and severe pain was 30% and 11%, respectively.<sup>20</sup> The incidence of these pain levels varied by analgesic technique: lower incidence was reported with patient-controlled and epidural analgesia compared with intramuscular analgesia.<sup>20</sup> In addition to the type of surgical procedure and analgesic/anesthetic intervention, other predictive factors of the severity of acute postoperative pain include younger age, female sex, preoperative pain, anxiety/mood, and incision size.<sup>21–28</sup> Finally, time after surgery also influences the frequency and severity of pain following surgery. In a Dutch study conducted in 1,490 surgical inpatients, 41% of patients reported moderate or severe pain on the day of surgery, with declining rates of 30%, 19%, 16%, and 14% seen on postoperative days 1, 2, 3, and 4, respectively.<sup>17</sup>

## Consequences of acute postoperative pain

Postoperative pain is not adequately managed in a significant proportion of patients, and is associated with a broad range of negative consequences, including increased morbidity, development of chronic postoperative pain, impaired function, recovery from surgery, and quality of life, prolonged opioid use, and increased medical costs.

## Morbidity

Inadequately managed acute postoperative pain is associated with effects related to aspects of both physiological and psychological function.<sup>29–32</sup> Changes can occur in diverse organ systems, including the cardiovascular (coronary ischemia, myocardial infarction), pulmonary (hypoventilation, decreased vital capacity, pulmonary infection), gastrointestinal (reduced motility, ileus, nausea, vomiting), and renal (increases in urinary retention and sphincter tone, oliguria) systems. A negative impact may also be seen on immune

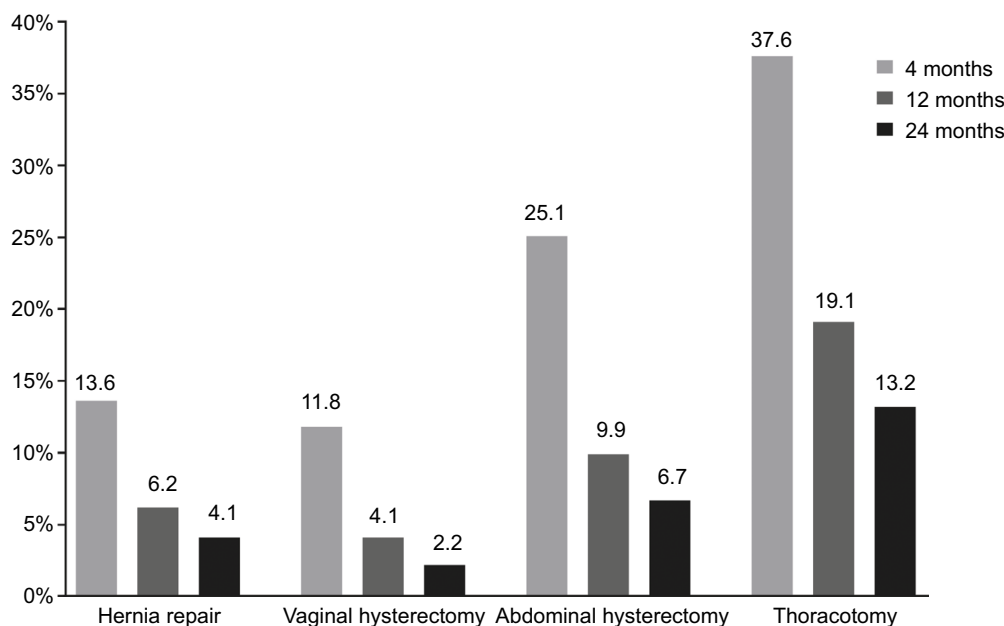
function, the muscular system, coagulation, and wound healing. Finally, poorly controlled pain after surgery may impair sleep and have negative psychological effects, such as demoralization and anxiety.

## Chronic postoperative pain

Poorly managed acute pain experienced after surgery may also result in the development of chronic pain. Based on reviews of the literature, persistent pain appears to affect between 10% and 60% of patients after common operations.<sup>33–38</sup> Fluctuations in reported incidence of chronic postsurgical pain are likely associated in part with the lack of a standardized definition of this complication, although it is frequently defined as enduring pain that has no other evident causes and lasts at least 2 months after surgery, ie, past the expected healing period.<sup>33,34,39</sup>

As with early pain, the prevalence of chronic postsurgical pain varies by type of surgery and generally decreases with time. In a 2-year, Spanish prospective cohort study of 2,929 patients who required hernia repair, thoracotomy, or hysterectomy, the incidence of chronic pain ranged from 37.6% (thoracotomy) to 11.8% (vaginal hysterectomy) at 4 months postsurgery (Figure 2).<sup>40</sup> In a French prospective cohort study of 2,397 patients who underwent cholecystectomy, inguinal herniorrhaphy, saphenectomy, sternotomy, thoracotomy, knee arthroscopy, breast cancer surgery, or elective cesarean section, the highest mean pain scores were observed after knee arthroscopy and thoracotomy, and the lowest after herniorrhaphy and cesarean section. The proportions of patients who reported persistent pain were 34.8% and 29.5% at 3 and 6 months after surgery, respectively.<sup>41</sup>

Over the last two decades, understanding of the mechanisms involved in the development of chronic pain has improved, with a combination of factors emerging as contributors, most notably inflammatory processes, tissue and nerve damage, and central sensitization.<sup>26,42–44</sup> The development of chronic pain after surgical intervention has been shown to involve preoperative, intraoperative, and postoperative factors.<sup>14,15,26,38,42,45–56</sup> Numerous studies of patients undergoing a broad variety of surgery types have demonstrated that the presence and intensity of acute postoperative pain are significant predictive risk factors for the development of chronic pain (Table 1).<sup>14,15,26,38,45–53,55,57–75</sup> A few studies have not found acute postoperative pain to be a significant predictor of chronic pain, but these conflicting findings may be linked to the studies' relatively small patient populations.<sup>46,54,76</sup> Other potential determinants of persistent pain after surgery include younger age, female sex, obesity,



**Figure 2** Incidence of chronic pain at 4, 12, and 24 months after surgery.

**Note:** Reprinted with permission from Montes A, Roca G, Sabate S, et al., Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study. *Anesthesiology*. 122(5):1123–41. <http://anesthesiology.pubs.asahq.org/Article.aspx?articleid=2135169>.<sup>40</sup>

smoking, genetic predisposition, preexisting pain, psychological factors (eg, preoperative anxiety and depression), and duration of surgery.<sup>14,15,26,33,38,40,48,53–55,57,73,77–87</sup>

## Impaired function, recovery, and quality of life

Postoperative pain also adversely affects physical functioning, recovery, and quality of life,<sup>54,55,88</sup> and its impact is correlated with the severity of pain.<sup>18,55,88</sup> Patients undergoing various types of elective surgery who had high levels of pain (pain score  $\geq 40$  on a 100 mm visual analog scale) 4 days postprocedure were shown to be at risk 6 months later for increased functional limitations (odds ratio [OR] 1.87, 95% CI 1.02–3.41)  $P=0.04$ ), poor global recovery (OR 2.61, 95% CI 1.47–4.62;  $P=0.001$ ), and impaired quality of life (aggregated Medical Outcomes Study Short-Form-36 [SF-36] quality of life score, standard  $\beta=-0.169$ ;  $P=0.001$ ).<sup>55</sup> Schulte et al found that physical function was worst at 3 months postthoracotomy, coinciding with peaks in pain scores at that time.<sup>89</sup> Similarly, 6 months after thoracic surgery, lung cancer-surgery patients had significantly worse scores for physical functioning, role functioning – physical, social functioning, and mental health compared with presurgical scores, which was largely attributed to significantly worse pain scores postsurgery.<sup>90</sup> In a large patient cohort, persistent pain occurring 3 months after thoracotomy was associated with significant reductions

in physical functioning and vitality scores on the SF-36, even though the pain was reportedly mild in most patients.<sup>91</sup>

In a Spanish prospective cohort study, Montes et al found that chronic postsurgical pain interfered with daily activities in 18% of patients after hernia repair or abdominal hysterectomy, 27% after vaginal hysterectomy, and 31% after thoracotomy at the 4-month follow-up visit.<sup>40</sup> In a similar Canadian study of chronic postoperative pain, nearly a third of patients described pain-related interference with sleep, mood, and enjoyment of life at even 6 months after gastrointestinal surgery.<sup>54</sup> Six weeks postoperatively, surgical patients had worse health-related quality of life than population norms in all domains measured, except mental health. Although improvement was observed by 6 months, quality of life in most domains, including physical function, general health, and vitality, remained significantly worse in the postsurgical pain cohort compared with norms. Postoperative pain was reported to affect activities of daily living adversely at 3 and 12 months postdischarge in approximately a quarter of patients who had had inpatient orthopedic surgery<sup>59</sup> and at 1 year postprocedure in nearly a third of patients who had had outpatient knee arthroscopy.<sup>46</sup> In an observational study of patients with chronic posttraumatic/postsurgical neuropathic pain, more severe pain was associated with significantly worse physical and mental health, general health status, and sleep outcomes, greater interference with function, and more depression and anxiety.<sup>92</sup>

**Table 1** Summary of prospective clinical studies ( $\geq 50$  patients) in which acute pain was found to be a risk factor for the development of persistent postoperative pain

Study	Surgical model	n	Findings
Fletcher et al <sup>60</sup>	18 different surgery types	3120	Percentage of time in severe pain on day 1 (OR 1.3, 95% CI 1.16–1.46; $P < 0.001$ )
Hoofwijk et al <sup>46</sup>	Outpatient surgery (10 specialties)	908	Acute postoperative pain (OR 1.62, 95% CI 1.02–2.58)
Peters et al <sup>55</sup>	Elective surgery (10 specialties)	625	High level of acute pain (score $\geq 40$ on 100 mm VAS, OR 3.21, 95% CI 1.64–6.3; $P = 0.001$ )
Choinière et al <sup>63</sup>	Cardiac surgery	1,247	Moderate–severe acute pain on postoperative day 3 (adjusted OR 2.67, 95% CI 1.74–4.11)
van Gulik et al <sup>68</sup>	Cardiac surgery via sternotomy	146	Severe pain (NRS $\geq 4$ ) on postoperative day 3 (OR 2.89, 95% CI 1.15–7.23, $P = 0.02$ )
Setälä et al <sup>15</sup>	Sternotomy	100	High pain score on postoperative day 1 was the most significant independent risk factor ( $P < 0.001$ )
Niraj et al <sup>75</sup>	Thoracotomy	306	82% of patients with $\geq 5$ episodes of severe pain within 72 hours of surgery had persistent postsurgical pain at 6 months
Hetmann et al <sup>61</sup>	Thoracotomy	106	Postoperative pain was significant in univariate analysis (OR 1.43, 95% CI 1.05–1.95, $P = 0.02$ )
Gotoda et al <sup>52</sup>	Thoracotomy	85	Pain on postsurgery day 1 (accounted for 12.4% of variance; $P = 0.0005$ )
Bisgaard et al <sup>71</sup>	Laparoscopic cholecystectomy	150	Total and maximum pain during the first week ( $P = 0.005$ )
Aasvang et al <sup>69</sup>	Herniotomy	464	30-day postoperative pain intensity ( $P = 0.0002$ )
Callesen et al <sup>72</sup>	Groin-hernia repair	466	High cumulative pain scores 1 week after surgery ( $P < 0.05$ )
Veal et al <sup>59</sup>	Orthopedic surgery	87	Average pain levels rated as moderate–severe at 10 days ( $P = 0.01$ ) and 6 weeks ( $P = 0.02$ )
Sayers et al <sup>74</sup>	Hip replacement	321	Acute postoperative pain at rest ( $\beta = 0.2$ , $P < 0.0002$ )
Thomazeau et al <sup>57</sup>	Knee replacement	104	High-intensity acute postoperative pain trajectory ( $P = 0.004$ )
Lavand'homme et al <sup>64</sup>	Knee arthroplasty	112	Higher acute-pain scores for maximal pain for days 1–8 ( $P < 0.05$ at all time points)
Masselin-Dubois et al <sup>49</sup>	Total knee and hip arthroplasty and breast surgery	189	Pain intensity on day 2 (OR 2.88, 95% CI 1.29–6.38; $P = 0.009$ )
Theunissen et al <sup>14</sup>	Hysterectomy	428	Acute postsurgical pain on day 4 ( $P < 0.05$ )
Pokkinen et al <sup>62</sup>	Hysterectomy	242	More severe pain in the first 20 postoperative hours was associated with a higher likelihood of persistent pain 6 months after hysterectomy
Pinto et al <sup>67</sup>	Hysterectomy	186	Acute postsurgical pain intensity at 48 hours ( $P < 0.001$ )
Brandsborg et al <sup>45</sup>	Hysterectomy	90	High acute postoperative pain intensity ( $P = 0.034$ )
VanDenKerkof et al <sup>48</sup>	Gynecologic	433	Moderate/severe in-hospital pain (RR 3, 95% CI 1–9.4)
Wang et al <sup>38</sup>	Breast cancer surgery	19,813 (30 studies)	Acute postoperative pain (OR 1.2, 95% CI 1.03–1.3 for each 1 cm on 10 cm VAS)
Andersen et al <sup>58</sup>	Breast cancer surgery	537	Acute postoperative pain (OR 2.8, $P = 0.0018$ )
Bruce et al <sup>47</sup>	Breast surgery	362	Acute postoperative pain at rest (OR 1.34, 95% CI 1.12–1.6; $P = 0.001$ )

**Abbreviations:** CI, confidence interval; OR, odds ratio; RR, relative risk; VAS, visual analog scale; NRS, numeric rating scale.

## Prolonged opioid use/opioid-induced adverse events

Worse pain at the surgical site on the day of surgery has been reported to be a significant predictor of persistent opioid use over 6 months in patients undergoing total knee or hip arthroplasty.<sup>93</sup> Using a large national-registry data set, Franklin et al found that greater pain reported 1 year after total-knee arthroplasty was associated with persistent opioid use 12 months postsurgery.<sup>94</sup>

Additionally, the consequences of poorly controlled pain during or after surgery may also include adverse effects of and toxicity related to anesthetic/analgesic medications, particularly if required for prolonged periods or at elevated doses to relieve pain. Although opioid analgesics remain the mainstay of postoperative pain therapy for efficacy, their use may be limited by potentially harmful effects. Common opioid-related AEs include respiratory depression, nausea, vomiting, pruritus, and bowel dysfunction, which have been



associated with a substantial burden on quality of life.<sup>95–101</sup> In addition, opioid-related AEs have an economic impact, as they have been shown to significantly increase hospital costs and length of stay.<sup>102</sup>

## Health economic impact

Inadequate pain relief has been shown to result in increased length of stay, time to discharge, readmission rates, and time before ambulation,<sup>31,103–107</sup> all of which can increase cost of care.<sup>104,108</sup> In a retrospective analysis of same-day surgeries, Coley et al observed that pain was the predominant reason for unexpected hospital admission or readmission postprocedure, reported in 38% of patients who returned for care.<sup>104</sup> The mean cost per patient for follow-up management of inadequately controlled pain after ambulatory surgery was estimated to be US\$1,869±\$4,553 per visit (1999 dollars).

In 2008 in the US, the annual cost to society of common chronic-pain conditions, including postoperative pain, was conservatively estimated to be in the range of \$560–\$635 billion.<sup>12</sup> These pain-related costs, which were based on health-care expenditure and lost productivity, were found to be higher than those related to heart disease, cancer, and diabetes. The cost of treating chronic pain that evolves from acute pain has been estimated to be as much as \$1 million per patient in a lifetime.<sup>108</sup>

## Improving postoperative pain: current and future options

Progress has been made in the recognition of pain after surgery as an important public health problem and in the investigation of associated mechanisms and risk factors. However, relatively little evidence is available on interventions that prevent or minimize this common surgical complication and improve patient outcomes. Given that a complex combination of pathways appears to be involved, reducing the frequency and intensity of perioperative pain and minimizing its impact after surgery, including its progression to persistent pain, may require a multifaceted approach. Surgical techniques that diminish the risk of tissue or nerve injury and inflammation should be selected when possible.<sup>109</sup> In addition, during the preoperative visit, identification of patients who may be prone to develop pain during or following surgery may allow for physical, emotional, and psychological preparations to mitigate surgical stress.<sup>110–112</sup>

Another fundamental strategy for pain prevention calls for more aggressive perioperative analgesic or anesthetic measures that decrease acute pain, minimizing noxious stimuli that induce peripheral and central sensitization.<sup>26,31,33,42,56,113–115</sup>

As reviewed elsewhere,<sup>7,42,116,117</sup> the benefits of preventive interventions remain largely theoretical, as none has yet been shown definitively to influence the incidence or severity of postoperative pain. Some promising findings nonetheless warrant brief description in the following sections.

## Local and regional anesthesia

Local anesthetics are frequently used during surgery as adjunctive therapy to manage acute pain and reduce analgesic consumption, but their effects on later postsurgical outcomes, including chronic postsurgical pain and quality of life, have been evaluated in a limited number of studies.<sup>6,116,118,119</sup> In a small, randomized, controlled study, significantly fewer patients treated with intravenous lidocaine during breast cancer surgery reported persistent pain at 3-month follow-up than patients who received saline.<sup>5</sup> However, evidence from several other studies assessing local anesthetics does not support their use as preventive therapy for chronic postoperative pain.<sup>120–126</sup> Contradictory findings have also been reported with regard to the impact of perioperative administration of adjunctive lidocaine therapy on quality of life after surgery. In a randomized, controlled study, patients undergoing complex spine surgery who were included in a lidocaine group reported significantly better quality of life 1 month postoperatively than those in the placebo group.<sup>119</sup> In contrast, in a similar study, spine-surgery patients who received lidocaine with intravenous anesthesia demonstrated no improvement in quality of life 1 month after surgery compared with those who received placebo.<sup>118</sup>

A Cochrane systematic review of 23 randomized, controlled trials compared the effects of local and regional anesthetics with those of conventional analgesia in preventing chronic postoperative pain.<sup>6</sup> Pooled results favored epidural anesthesia after thoracotomy (OR 0.33, 95% CI 0.2–0.56) and paravertebral block after breast cancer surgery (OR 0.37, 95% CI 0.14–0.94) in reducing the risk of pain at 6 months. However, these data should be interpreted with caution, because of the small populations, methodological shortcomings, and incomplete outcome reporting of many of the included studies.

## Nonopioid analgesics

Several classes of nonopioid pharmacological agents that target pain via differing pathways have been evaluated as means of improving postoperative outcomes, although the research remains limited. In three prospective, randomized trials, patients receiving the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen or the COX2 inhibitor parecoxib

did not achieve significant reduction in persistent pain after surgery.<sup>127–129</sup> Based on a systematic review/meta-analysis of 14 randomized controlled trials of the uncompetitive *N*-methyl-D-aspartate (NMDA)-receptor antagonist ketamine in various surgical models, Chaparro et al reported that treatment with this agent provided a significant but small decrease in the incidence of pain 3 months or more after surgery, although possible overestimation of treatment effect was noted because of the studies' small patient populations.<sup>7</sup> However, researchers conducting two more recent systematic reviews concluded that available evidence did not support the effectiveness of perioperative administration of ketamine in reducing chronic pain after surgery.<sup>130,131</sup> In a randomized, controlled pilot study of the preventive effects of ketamine on postmastectomy pain syndrome, when administered during surgery, this agent did not influence the incidence of persistent pain or quality of life for 3 months postsurgery.<sup>132</sup>

Similarly, although encouraging data from individual trials have been reported, systematic reviews of clinical trials of the 3-alkylated  $\gamma$ -aminobutyric acid analogs gabapentin and pregabalin have not consistently or unequivocally demonstrated reductions in the incidence or intensity of persistent postsurgical pain with these antiepileptic agents.<sup>7,116,130</sup> However, in a small, randomized, controlled study, 3 months after major spine surgery, greater improvement in quality of life was reported by patients who received oral pregabalin versus placebo when administered 1 hour preoperatively and for 48 hours postoperatively, in addition to continuous infusion of morphine and ketorolac tromethamine.<sup>133</sup> In addition, perioperative pregabalin was associated with improved functional outcomes 3 months postoperatively in patients who underwent spinal surgery under general anesthesia.<sup>134</sup>

The selective norepinephrine and serotonin-reuptake inhibitor venlafaxine has been shown significantly to reduce the incidence and intensity of pain 6 months after breast cancer surgery compared with placebo and gabapentin.<sup>135</sup> Additionally, the perioperative administration of another antidepressant with this mechanism of action, duloxetine, as part of a multimodal regimen in women undergoing abdominal hysterectomy significantly improved postoperative quality of recovery.<sup>136</sup> In a randomized, controlled study of patients undergoing coronary revascularization, administration of the selective serotonin-reuptake inhibitor escitalopram administered 2–3 weeks before surgery to 6 months after surgery provided more rapid improvement in mental health aspects of quality of life in all patients and reduced postoperative pain in patients who reported preoperative depression.<sup>137</sup> Although

promising, additional research is needed to determine the efficacy of antidepressants as preventive therapy postsurgery.

## Opioid analgesics

Conventional opioids, such as morphine, hydrocodone, and fentanyl, continue to be considered the “gold standards” of postoperative pain management, largely because they are very effective analgesics that are available in a broad range of formulations. These agents nonetheless have well-recognized limitations, including a narrow therapeutic window, with a relatively small range of doses providing adequate pain relief without resulting in undesirable AEs or toxicity. Certain patient subgroups, including patients who are older, obese, smoke, or have sleep apnea, may be at particular risk of opioid-related respiratory depression and excessive sedation. The narrow therapeutic range of conventional opioids, which bind to  $\mu$ -opioid receptors, may be associated with their unselective activation of two intracellular signaling pathways: the G-protein pathway and the  $\beta$ -arrestin pathway.<sup>138</sup> Preclinical studies have shown that G-protein pathway activation distal to the  $\mu$ -receptor results in analgesia; however,  $\beta$ -arrestin pathway activation is associated with opioid-related AEs, such as constipation and respiratory depression, as well as inhibition of G-protein-mediated analgesia.<sup>138–143</sup>

Three new opioids, which are currently in development, have a novel mechanism of action for relieving acute postoperative pain that is based on a differential signaling approach. These agents modulate  $\mu$ -receptor activity by selectively engaging intracellular pathways associated with analgesia (G protein) rather than those associated with adverse effects ( $\beta$ -arrestin), thereby potentially improving the balance between pain control and tolerability.<sup>138</sup> With a potentially expanded therapeutic window, these agents may more effectively relieve acute postoperative pain and reduce the consequences of poorly controlled pain, including its progression to chronic postoperative pain.

PZM21, a selective  $\mu$ -opioid-receptor agonist, has been shown potentially to activate G-protein pathway signaling, with minimal  $\beta$ -arrestin 2 recruitment.<sup>9</sup> In preclinical studies, G-protein-mediated action of PZM21 on  $\mu$ -receptor activity provided analgesia with an improved AE profile (eg, reduced constipation and respiratory depression) compared with morphine at equianalgesic doses; no activity was observed on reflexive pain responses mediated through the spinal cord. Mitragynine pseudoindoxyl, an oxidative rearrangement product of the corynanthe alkaloid mitragynine (isolated from the Southeast Asian plant *Mitragyna speciosa*), is a  $\mu$ -opioid-

receptor agonist and  $\delta$ -receptor antagonist with differential signaling properties.<sup>8</sup> In preclinical studies, mitragynine had high affinity at the  $\mu$ -receptor and produced analgesia; it did not recruit  $\beta$ -arrestin and resulted in minimal respiratory depression and less constipation than morphine.

Oliceridine (TRV130) is a novel  $\mu$ -receptor G-protein pathway-selective modulator that differentially activates G-protein coupling while limiting  $\beta$ -arrestin recruitment.<sup>144,145</sup> In Phase II clinical studies conducted in patients with moderate–severe acute pain after bunionectomy or abdominoplasty, oliceridine administered in either fixed or flexible (as needed) doses provided significantly greater reductions in pain scores than placebo and similar but more rapid analgesia than morphine.<sup>10,11</sup> In the abdominoplasty study, oliceridine-treated patients reported no serious AEs and had fewer opioid-related AEs, such as nausea, vomiting, and respiratory depression, than morphine-treated patients.<sup>11</sup> Although findings from studies of these novel opioid analgesics are also encouraging, additional research is needed to examine whether they improve patient outcomes, such as quality of life, or prevent the evolution to chronic pain because they potentially provide more effective control of acute postoperative pain.

## Multimodal analgesia

Since this concept's introduction in 1993,<sup>146</sup> the combined use of local and regional anesthetics, different classes of nonopioid pharmacologic agents, such as NSAIDs, COX2 inhibitors, NMDA-receptor antagonists, and antiepileptics, and opioid analgesics, has become a widely accepted means of reducing acute postoperative pain while limiting perioperative opioid consumption and opioid-related AEs. Insufficient research is available, but some individual clinical trials have demonstrated a decreased incidence of chronic postoperative pain when multimodal regimens are used to manage pain during surgery.<sup>116,147–150</sup> Given the increased use of multimodal approaches over the past two decades, future studies clearly must address their effects beyond opioid sparing in reducing early postsurgical pain and its consequences.

## Conclusion

Postoperative pain continues to be inadequately managed in a surprising proportion of patients, and is associated with numerous negative clinical, patient-reported, and health economic outcomes. Importantly, poorly controlled acute pain after surgery has been consistently shown to be a predictive factor for the development of chronic pain. More effective analgesic/anesthetic perioperative measures may help prevent

the adverse consequences of poorly controlled pain, including its transition to persistent pain. Preliminary evidence from studies of local and regional anesthetics, nonopioid analgesics, such as NSAIDs, COX2 inhibitors, NMDA-receptor antagonists, and antiepileptic and antidepressant agents, suggests potential benefit, but is inconsistent and insufficiently robust to prompt a modified approach. Conventional opioid therapies remain the mainstay of postoperative pain management, but opioid analgesic use involves the challenging pursuit of an acceptable balance between effective pain control and harmful side effects. Pain control with conventional opioids can be suboptimal, due to a narrow therapeutic window, which may be associated with their unselective mechanism of action. New selective  $\mu$ -opioid agonists, such as PZM21 and oliceridine, which have differential  $\mu$ -receptor downstream signaling compared with conventional opioids, may help to optimize acute-pain management by providing a wider therapeutic window, allowing for potent analgesia with fewer safety and tolerability concerns. Large-scale, well-controlled studies are needed to determine if currently available treatment approaches, including multimodal regimens or novel therapies, such as selective  $\mu$ -opioid-receptor agonists, used during surgery or prior to discharge reduce the negative impact of inadequate pain relief.

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