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## Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic

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### Abstract

Physicians, policymakers, and researchers are increasingly focused on finding ways to decrease opioid use and overdose in the United States both of which have sharply increased over the past decade. While many efforts are focused on the management of chronic pain, the use of opioids in

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surgical patients presents a particularly challenging problem requiring clinicians to balance two competing interests: managing acute pain in the immediate postoperative period and minimizing the risks of persistent opioid use following the surgery. Finding ways to minimize this risk is particularly salient in light of a growing literature suggesting that post-surgical patients are at increased risk for chronic opioid use. The perioperative care team, including surgeons and anesthesiologists, is poised to develop clinical and systems-based interventions aimed at providing pain relief in the immediate postoperative period while also reducing the risks of opioid use longer term. In this paper, we discuss the consequences of chronic opioid use following surgery, and present an analysis of the extent to which surgery has been associated with chronic opioid use. We follow with a discussion of the risk factors that are associated with chronic opioid use after surgery, and proceed with an analysis of the extent to which opioid sparing perioperative interventions (e.g., nerve blockade) have been shown to reduce the risk of chronic opioid use following surgery. We then conclude with a discussion of future research directions.

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## Introduction

The U.S. is facing an opioid crisis as the rate of opioid overdoses has roughly tripled since 1999, and continues to climb.<sup>1</sup> At present, the most commonly prescribed opioids, oxycodone and hydrocodone, are also the most commonly involved opioids in overdose deaths.<sup>1</sup> Opioid prescribing has quadrupled since 1999, and has risen in parallel with the number of overdoses from the most commonly prescribed opioids.<sup>1</sup> The economic cost of prescription opioid-related overdose, abuse and dependence exceeds \$78.5 billion annually with the majority of costs related to health care, substance abuse treatment, and lost productivity.<sup>2</sup> To address this opioid crisis, a collaborative effort of stakeholders including law enforcement, the general public, and healthcare providers is needed to encourage appropriate opioid prescribing and monitoring for misuse, abuse, and diversion; expand prescription drug monitoring programs; and widen access to rescue naloxone and opioid use disorder treatment programs.

A particularly difficult aspect of this crisis is the use of opioids among surgical patients. Approximately 51 million Americans undergo inpatient surgery annually, and opioids remain a primary modality for postoperative acute pain management.<sup>3-8</sup> Over 80% of patients receive opioids after low-risk surgery, and over 80% of these prescriptions involve oxycodone or hydrocodone.<sup>8</sup> Thus, surgical patients routinely receive the most commonly prescribed opioids that are also most commonly implicated in drug overdose deaths. In the inpatient setting, patients undergoing operations most often receive a variety of opioids administered through multiple routes, and the majority of patients prescribed opioids at hospital discharge have had surgery.<sup>9,10</sup> Surgery represents a critical event where the majority of patients are exposed to opioids regardless of whether or not they have had a prior opioid-related adverse event including overdose.<sup>1,11</sup> Opioid tolerant patients typically require higher doses over extended postoperative periods further compounding the risks of persistent opioid use, misuse, addiction, and overdose.<sup>12-17</sup> Thus, tangible risks exist for both opioid-naïve and opioid-tolerant patients undergoing surgery.

The perioperative care team, including anesthesiologists, now face the challenge of optimizing perioperative pain management while limiting the impact of prescription opioid exposure both in the hospital and long after discharge. Through interdisciplinary collaboration with primary care providers, surgeons, and other specialists, anesthesiologists now have the opportunity to provide the bridge between acute inpatient care and remote outpatient recovery, which will serve a critical role to optimize the safety of all surgical patients who are exposed to prescription opioids.

## Risks Associated with Opioid Use after Surgery

The adverse effects of prescription opioids are well documented. The presence of tolerance and physical dependence can occur even at prescribed doses.<sup>18–23</sup> Opioids are associated with immunosuppression and opioid-induced endocrinopathy (sexual dysfunction, depression, decreased energy).<sup>24–30</sup> Opioids are implicated in opioid-induced hyperalgesia or increased pain sensitivity despite increasing doses of opioids. This hyperalgesia has been demonstrated with exposure to both short- and long-term opioids.<sup>31–33</sup>

Opioid-related adverse effects can manifest as a multitude of symptoms after surgery ranging from sedation, respiratory depression, delirium, ileus, to the paradoxical worsening of pain with higher opioid doses. The significance of these opioid-related adverse effects cannot be understated. The primary mechanism of opioid fatality involves opioid-induced respiratory depression and subsequent hypoxia, hypercapnia, and cardiorespiratory arrest.<sup>34–36</sup> Pulmonary conditions such as chronic obstructive pulmonary disease, and concurrent use of CNS depressants including benzodiazepines or antidepressants potentiate the risk of opioid-induced respiratory depression and overdose after surgery.<sup>37–40</sup> Postoperative opioid-induced respiratory depression often occurs within the first 24 hours, and leads to death or severe brain damage in the majority of patients.<sup>41</sup> Thus, measures to limit postoperative opioid use may help to decrease the morbidity and mortality resulting from opioid-related adverse events. These adverse effects are likely to accumulate as patients take opioids for longer lengths of time after surgery.

Particularly concerning, is the association between preoperative opioid use and increased postoperative morbidity and mortality. In a cohort of 200,005 patients undergoing elective surgery, 8.8% of patients were using opioids prior to surgery,<sup>42</sup> preoperative opioid use was associated with longer hospital stays, a higher rate of 30-day readmission, and increased healthcare expenditures at 90-, 180-, and 365 days after surgery.<sup>42</sup> Similarly, long-term opioid use was associated with an increased risk of knee revision in the first year following total knee arthroplasty in a cohort of veterans.<sup>43</sup> As patients taking opioids prior to surgery often require higher postoperative doses for extended periods of time, it is possible that these heightened postoperative opioid requirements increase vulnerability to a multitude of opioid-related adverse effects. Alternatively, chronic opioid use may be associated with a number of psychosocial characteristics that impede physical function and recovery after surgery.

Concerns regarding persistent opioid use after surgery include misuse, abuse, addiction and diversion. Of patients surveyed in outpatient neurosurgery or orthopedic clinics of a tertiary academic medical center, 14.7% reported using opioids without a prescription, in greater

amounts, or longer than prescribed, far exceeding the national prevalence of opioid misuse of 1.9% amongst US adults.<sup>44</sup> The potential for misuse and diversion is highlighted by research reporting that the majority of patients keep their unused opioids rather than disposing of them after surgery.<sup>45–47</sup> As provider overprescribing for acute pain is a primary source of diversion in America,<sup>48</sup> efforts to limit excess perioperative opioid prescribing may be warranted.

Serious consequences of perioperative opioid misuse and dependence include increased inpatient mortality (OR 3.7, 95% CI 2.7–5.1), aggregate morbidity (OR 2.3, 95% CI 2.2–2.4), and resource utilization.<sup>49</sup> In a cohort of patients scheduled for a variety of operations (thoracotomy, total knee replacement, total hip replacement, radical mastectomy, and lumpectomy), preoperative opioid use was associated with an increased risk for opioid misuse after surgery.<sup>50</sup> Future work to characterize risks factors for the transition from therapeutic use to misuse are warranted in patients undergoing surgery given the increased morbidity, mortality, and healthcare costs associated with perioperative opioid misuse.

### Persistent or Chronic Opioid Use After Surgery

Opioids prescribed during and after surgery may trigger long-term use in patients regardless of whether or not they are opioid-tolerant, taking opioids regularly prior to surgery, or ever been exposed to opioids in the past.<sup>44,47,51–54</sup> Even opioids prescribed for low-pain, outpatient, or short-stay surgeries increase the risk of persistent opioid use,<sup>51,52</sup> and over 60% of people receiving 90 days of continuous opioid therapy remain on opioids years later.<sup>55</sup> Patients receiving an opioid prescription after short-stay surgeries have a 44% increased risk of long-term opioid use.<sup>52</sup> Even prescribing opioids at hospital discharge to previously opioid naïve patients is a risk factor for chronic opioid use 1 year after discharge (AOR=4.9, 95% CI 3.22–7.45).<sup>10</sup> Surgery is an important stimulus for chronic opioid use even amongst those who are opioid naïve prior to surgery.<sup>56</sup> Given the likely transition from acute to long-term opioid use after surgery, measures to curb the duration of postoperative opioid use may be necessary to limit the risks of perioperative opioid exposure.

The incidence of prolonged opioid use after surgery varies based on preoperative patient characteristics and the type of surgery a patient undergoes. In a retrospective analysis of 641,941 opioid naïve patients undergoing surgery, and 18,011,137 opioid naïve nonsurgical patients, the incidence of chronic opioid use amongst non-surgical patients was 0.136% (95% CI, 0.134%–0.137%).<sup>56</sup> The highest incidence of chronic opioid use occurred after total knee arthroplasty (1.41%, 95% CI, 1.29%–1.53%).<sup>56</sup> After controlling for age, sex, and preoperative medication use (antidepressants, antipsychotics, benzodiazepines), patients undergoing total knee arthroplasty, open cholecystectomy, total hip arthroplasty, simple mastectomy, laparoscopic cholecystectomy, open appendectomy, and cesarean delivery were at significantly increased risk for chronic opioid use after surgery.<sup>56</sup> Risk factors for chronic opioid use after surgery amongst opioid naïve patients included male sex, age greater than 50 years, preoperative use of benzodiazepines, preoperative use of antidepressants, depression history, alcohol abuse history, and drug abuse history.<sup>56</sup> Similarly, in a retrospective cohort of 36,177 opioid naïve patients undergoing minor (e.g. varicose vein removal, laparoscopic cholecystectomy, laparoscopic appendectomy, hemorrhoidectomy,

thyroidectomy, transurethral prostate surgery, parathyroidectomy, and carpal tunnel surgery) or major (e.g. ventral incisional hernia repair, colectomy, reflux surgery, bariatric surgery, and hysterectomy) operations, the rates of new persistent opioid use varied between 5.9–6.5%.<sup>57</sup> The incidence in a non-operative control cohort was only 0.4%. Risks factors for new persistent opioid use after surgery included preoperative tobacco use, alcohol and substance abuse disorders, mood disorders, anxiety, and preoperative pain disorders.<sup>57</sup> The higher incidence of new persistent opioid use noted in this second study may relate to defining the outcome as any opioid prescription filled between 90 and 180 days after the surgical procedure,<sup>57</sup> whereas the first study defined chronic opioid use as 10 or more prescriptions, or more than a 120 days' supply of an opioid within the first year following surgery excluding the first 90 days.<sup>56</sup>

Regardless of whether or not patients are taking opioids prior to surgery, undergoing surgery in and of itself is a risk factor for instigating persistent and chronic opioid use after surgery. When examining the surgical population as a whole, including patients taking opioids prior to surgery, postoperative chronic opioid use ranges from 9.2 to 13%.<sup>58,59</sup> In the context of the current opioid crisis, measures to decrease the overall prevalence of chronic opioid use after surgery will decrease opioid-related adverse events including opioid misuse, abuse, addiction, diversion, respiratory depression and overdose.

## Predictors of Chronic Opioid Use After Surgery

Preoperative opioid use is an important risk factor for persistent or chronic opioid use after surgery. In a national, population-based study of patients undergoing upper extremity surgery, opioid use prior to surgery was associated with longer opioid prescriptions, and more refills after surgery.<sup>60</sup> Patients using opioids prior to operations including bariatric surgery, lumbar fusion, total joint arthroplasty, and kidney transplantation are at increased risk for chronic postoperative opioid use.<sup>61–65</sup> Between 64 to 77% of chronic opioid users prior to surgery continue chronic opioid use after surgery.<sup>62,63</sup> In a perioperative model of time to postoperative opioid and pain cessation using Cox regression, legitimate preoperative opioid use was a risk factor for persistent opioid use in a mixed surgical cohort.<sup>66</sup> Higher preoperative opioid doses lead to an incremental risk of chronic use after surgery. Patients taking greater than 60mg oral morphine equivalents preoperatively have an 80% likelihood of chronic use 6 months after total knee or hip arthroplasty.<sup>67</sup>

Additional risk factors for postoperative chronic opioid use include lower socioeconomic status, preoperative pain, medical comorbidities (e.g. pulmonary disease, heart failure), depression, and a history of drug, alcohol, or tobacco abuse.<sup>56,59</sup> Use of specific medications including preoperative benzodiazepines and antidepressants are also associated with persistent opioid use after surgery.<sup>54,56,59</sup>

Prior research highlights preoperative depression and use of antidepressants as important risk factors for chronic opioid use after surgery.<sup>56,59</sup> Clinically diagnosed depression (rather than anxiety or adjustment disorders), increases the odds of chronic opioid therapy after lumbar fusion (OR 2.34,  $p < 0.001$ ), and 77% of patients with depression receive chronic opioid therapy after lumbar fusion compared to 50% without a depression diagnosis.<sup>64</sup>

Similarly, depression is a risk factor for new chronic opioid use after total hip arthroplasty rather than anxiety or psychoses.<sup>68</sup> This mirrors trends in long-term opioid therapy for non-cancer pain, as patients with a history of depression are more likely to receive chronic opioid therapy at higher daily doses, and for extended durations.<sup>69</sup> In a mixed surgical cohort, elevated preoperative Beck Depression Inventory-II (BDI-II) scores were a significant predictor of prolonged opioid use independent of pain in a mixed surgical cohort.<sup>66</sup> Further factor analysis identified self-loathing symptoms of the BDI-II as a significant predictor of prolonged opioid use rather than somatic symptoms, which could be confounded by pain and other medical comorbidities in a surgical cohort.<sup>70–72</sup> The primary determinants of postoperative opioid cessation appear unrelated to the duration of postoperative pain and preoperative pain intensity both at the future surgical site and elsewhere over the entire body.<sup>66</sup> Thus, specific efforts to promote opioid cessation are warranted aside from focusing solely on optimizing pain management in the postoperative period.

## Strategies to Promote Opioid Cessation After Surgery

### Regional and Neuraxial Anesthesia

Nerve blockade of peripheral nerves (regional anesthesia) or the central nervous system (neuraxial anesthesia) has been proposed as a possible way of reducing the risk of persistent opioid use following surgery. Nerve blockade could reduce the risk of persistent postoperative opioid use through one of two mechanisms. The first, a theory known as preventative analgesia,<sup>73–75</sup> suggests that nerve blockade can prevent the transition from acute to chronic pain by directly blocking transmission of pain impulses during the perioperative period and thereby preventing central sensitization and chronic neuropathic pain. Second, nerve blocks are a well-established modality for treating acute post-operative pain, which when severe, is predictive of the development of chronic pain.<sup>76</sup>

Despite these theoretical benefits and several studies showing that nerve blockade is associated with reduced opioid requirements in the immediate postoperative period,<sup>77–79</sup> whether nerve blockade reduces long term opioid use following in practice remains unclear. A meta-analysis of 23 randomized control trials found that epidural anesthesia was associated with decreased persistent postoperative pain for patients undergoing thoracotomy and that paravertebral blocks were associated with decreased persistent postoperative pain for breast cancer surgery.<sup>80</sup> However, while these studies suggest that nerve blocks are associated with a decreased risk for persistent postoperative *pain*, whether nerve blocks decrease persistent postoperative opioid use itself remains an open question. Indeed, recent observational studies have found no association between nerve blockade and the risk of persistent postoperative opioid use for patients undergoing abdominal surgery,<sup>81</sup> total knee arthroplasty,<sup>82</sup> or shoulder arthroplasty.<sup>83</sup>

### Intravenous Local Anesthetic

There is increasing interest in the intraoperative use of intravenous local anesthetics—typically lidocaine—for the purpose of reducing perioperative opioid consumption. When given as part of a nerve block, local anesthetics exert an analgesic effect by blocking the sodium channels responsible for neural transmission of pain impulses. The effect of



*intravenous* local anesthetics on opioid consumption is thought to occur via the blockade of pro-inflammatory responses to surgery.<sup>84–86</sup> A recent review found that intravenous lidocaine was associated with decreased opioid requirements in the immediate perioperative period for a variety of surgeries (e.g. abdominal and thoracic procedures), although the literature suggested no benefit in some others (e.g., total hip arthroplasty).<sup>84</sup> With regards to longer-term outcomes, two studies found that intraoperative lidocaine use was associated with decreased chronic pain at three<sup>87</sup> and six months<sup>88</sup> post-procedure for patients undergoing mastectomy, while another study found improved quality of life scores at three months following spine surgery.<sup>89</sup> The duration of follow-up for all three studies was fairly short (maximum six months post-procedure), and while the three studies examined the incidence of persistent postoperative *pain*, none of the three studies directly measured opioid use itself. More research is needed to characterize the extent to which the perioperative use of intravenous local anesthetics can reduce persistent opioid use following surgery.

### Other Nonopioid medications

Numerous studies have examined whether the intraoperative use of non-opioid medications with analgesic properties is associated with decreased opioid consumption following surgery. Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist frequently used for induction. Its analgesic properties as a NMDA receptor antagonist have led researchers to examine whether its intraoperative use is associated with reduced opioid consumption. While studies have generally found intraoperative ketamine to be associated with decreased opioid consumption in the immediate postoperative period and for up to six weeks post-procedure,<sup>90–92</sup> to date no studies have examined its effect on opioid consumption at longer time windows following surgery.

Acetaminophen is frequently used for pain management or as part of multimodal analgesia protocols. As with ketamine, while numerous studies suggest that it is associated with decreased opioid consumption in the immediate perioperative period,<sup>93,94</sup> there is a lack of research examining its effectiveness at reducing opioid usage in the longer term.

Perioperative gabapentin appears to reduce the incidence and intensity of postoperative pain up to 6 months after otolaryngology, orthopedic, mastectomy, and abdominal/pelvic operations.<sup>95–98</sup> Furthermore, perioperative gabapentin is often cited as a component of multimodal analgesia,<sup>99</sup> but results have been mixed regarding gabapentin's efficacy to reduce acute pain in the context of multimodal analgesia. Usual care varies across operations and hospitals nationwide.<sup>100–104</sup> Previous trials examining gabapentin's effect on opioid consumption have reported immediate reductions in 24 to 72 hours postoperative use during hospital admission.<sup>101,102,105</sup> In contrast, a meta-analysis of 9498 patients found a negligible reduction in 24-hour morphine consumption with use of gabapentin, with an even more diminished effect in the context of multimodal analgesia.<sup>106</sup> These findings were limited by low quality evidence due to small study sizes and inconsistency.<sup>106</sup> Studies examining the utility of perioperative gabapentin for remote postoperative opioid cessation are needed to fully understand the utility of gabapentin alone or as part of multimodal analgesia protocols.

## Multimodal Analgesia

Multimodal analgesia consists of 2 or more medications or non-pharmacologic interventions (e.g. transcutaneous electrical nerve stimulation) with varying mechanisms of action for postoperative pain relief.<sup>99</sup> Components of multimodal analgesia often include gabapentinoids, acetaminophen, ketamine, NSAIDs, and regional anesthesia.<sup>107</sup> It is thought that the combination of treatments is likely to have an additive or synergistic effect on opioid-sparing as well. In a meta-analysis of 52 randomized trials including 4,893 adults, acetaminophen, NSAIDs, or selective COX-2 inhibitors significantly reduced 24-hour morphine consumption after surgery.<sup>108</sup> Similarly, a systematic review found that co-administration of paracetamol, NSAIDs, and COX-2 inhibitors with opioids decreases 24-hour postoperative morphine consumption without a clear benefit of one category vs. another in terms of adverse effects.<sup>109</sup> Future studies examining extended multimodal analgesic techniques with post-operative follow-up long after hospital discharge are needed to determine the utility of multimodal analgesia in preventing chronic opioid use after surgery. Furthermore, given the significant variation in implementing multimodal analgesia techniques across the U.S., randomized trials are needed to inform best practices for clinical care.<sup>104</sup>

## Future Directions

Multiple professional societies have focused efforts on reducing prescription opioid exposure after surgery. Guidelines now strongly recommend instituting a plan for opioid tapering after surgery. For example, the Agency Medical Directors' Group Interagency Guidelines on Prescribing Opioids for Pain recommend tapering opioids by 6 weeks after most major surgeries to preoperative doses or lower in the absence of clinically meaningful improvements in function and pain, with 20% weekly dose reductions.<sup>110</sup> However, the standard of care is to advise patients to discontinue opioids when they no longer have pain, and patients usually self-taper their opioids with minimal instructions after surgery.

There are efforts focused on providers' prescribing patterns. This is being done by providing recommendations on number of pills or limiting the number prescribed. Currently a disconnect exists between opioids prescribed and opioids used after surgery. The amount prescribed does not influence patients' decisions to continue or discontinue opioid use, and patients exhibit wide variability in opioid needs after similar procedures.<sup>2,47,59,60</sup> Research is needed to address a critical knowledge gap regarding optimal mechanisms for postoperative opioid weaning with supportive psychosocial interventions in the form of randomized controlled trials to support expert opinion.<sup>111</sup> Evidence and evaluation of new programs is required to ensure the best balance of pain control with minimal opioid exposure.

In addition, a targeted approach is needed for vulnerable subsets of patients who are at elevated risk for chronic opioid use after surgery. For example, patients with elevated preoperative depressive symptoms may benefit from preoperative and ongoing postoperative cognitive behavioral therapy, to help curb postoperative opioid use and improve functional outcomes after surgery. Similarly, future studies examining extended multimodal analgesic techniques with post-operative follow-up long after hospital discharge are needed to



determine the utility of multimodal analgesia in preventing chronic opioid use after surgery. With the advent of novel regional anesthetic techniques and medications, perioperative research must extend beyond hospital discharge to characterize the efficacy of these strategies in promoting opioid cessation.

Another vulnerable group of patients are those taking opioids prior to surgery. Given the association between preoperative opioid use and increased postoperative morbidity and mortality, research is needed to understand the mechanisms driving these worse outcomes. It is not entirely clear whether additional confounding patient characteristics are driving these prior research findings. In addition, interventions such as preoperative opioid tapering should be studied in the context of surgical outcomes and opioid use after surgery. If effective, the ideal time frame for opioid tapering prior to surgery would also need to be identified.

With continued opioid use after surgery, the risk of postoperative opioid-induced respiratory depression remains. Given the significant morbidity and mortality associated with opioid-induced respiratory depression, measures are needed to limit its occurrence. Opioid overdose education and naloxone distribution provides patients with education on opioid overdose prevention, recognition of opioid overdose, and training on the rescue response, including provision of naloxone.<sup>112</sup> In conjunction with measures to limit the duration and dosages of opioids prescribed after surgery, future work to study the implementation of perioperative opioid overdose education and naloxone distribution to high-risk surgical patients may promote safer opioid use and prevent significant opioid-related adverse effects.

Although persistent opioid use after surgery may lead to misuse, abuse, addiction, and diversion. More perioperative research is needed to characterize the transition from postoperative therapeutic use to misuse of prescription opioids. The potential to improve patient outcomes is apparent as perioperative opioid misuse is associated with increase morbidity, mortality, and healthcare costs. Furthermore, longitudinal follow-up to examine the initiation of illicit heroin or fentanyl in patients misusing prescription opioids is needed to understand the contribution of perioperative opioid misuse to the ongoing opioid epidemic. Given the potential for overprescribing and diversion, patient education and measures to promote safe storage and disposal of prescription opioids must be further implemented after surgery.

## Conclusions

In the context of the current opioid epidemic in the U.S., healthcare providers are now faced with the challenge of simultaneously optimizing postoperative pain management and limiting opioid use after surgery. Emerging data suggests that persistent and chronic opioid use after surgery is a rising complication amongst both opioid naïve patients and those taking opioids preoperatively. Modifiable risk factors for chronic opioid use after surgery should be clearly delineated and targeted with novel interventions. In addition, existing interventions exhibiting opioid-sparing effects within the immediate postoperative period should be examined in randomized trials with follow-up long after hospital discharge to determine their utility in promoting definitive opioid cessation after surgery. Evidence-based

strategies for opioid tapering are needed to complement the burgeoning guidelines and expert opinions advocating for postoperative opioid tapering to optimize patient success, prevent under-prescribing of opioids to patients, and prevent opioid misuse and diversion.

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