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ACUTE PAIN MEDICINE (R URMAN, SECTION EDITOR)

Gabapentinoid Use in Perioperative Care and Current Controversies

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Abstract

Purpose of Review This review summarizes the risks and benefits of gabapentinoids (gabapentin and pregabalin) for perioperative pain control and the controversies surrounding their use in a variety of settings. We review current literature with the goal of providing patient-centric and procedure-specific recommendations for the use of these medications.

Recent Findings Gabapentinoids are among the most prescribed medications in the USA, and typically for off-label indications such as postoperative pain. In the perioperative setting, multimodal analgesic or "opioid-sparing" regimens have become the standard of care—and some clinical protocols include gabapentinoids. At the same time, guidelines regarding the perioperative use of gabapentinoids are conflicting and evidence supporting their broad use is lacking.

Summary Gabapentinoids administered perioperatively reduce opioid requirements and pain scores for a variety of surgeries. The extent of opioid and pain reduction, however, is not always clinically significant. These medications reduce postoperative nausea and vomiting as well as pruritis, likely as a feature of reducing opioid intake, but are associated with side effects such as dizziness, ataxia, and cognitive dysfunction. Gabapentinoids also increase the risk of respiratory depression, in particular when paired with opioids. There is thus evidence suggesting that the *routine* use of these medications for perioperative pain management is not recommended. An individualized, patient- and surgery-specific approach should be used, although research is still needed to determine risks and benefits during perioperative use.

Keywords Gabapentin · Pregabalin · Multimodal · ERAS · Opioid epidemic

Introduction

Adequate pain control is an essential component of protocols for enhanced recovery after surgery (ERAS) pathways [1]. Despite an increasing emphasis on pain management and advances in pain medicine, intense pain after surgery remains a common occurrence, with most patients postoperatively experiencing moderate or severe pain [2]. The presence of poorly controlled postoperative pain can have deleterious effects on multiple aspects of patient recovery and may also increase the risk of persistent postsurgical pain [3]. Historically, and in particular in the USA, opioids have been a mainstay in the management of acute and chronic pain, although there has in recent years been an increasing awareness of the risks associated with chronic opioid use and factors associated with new persistent opioid use [4–7]. Not surprisingly, with this awareness there is an increased interest in multimodal, opioid-sparing analgesia.

Gabapentinoids (gabapentin and pregabalin) bear a structural resemblance to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but its activity is thought to be not at $GABA_A$ or $GABA_B$ receptors but rather at the α-2-δ subunit of presynaptic voltage-dependent calcium channels, ultimately modulating the release of excitatory neurotransmitters involved in seizures and nociception [8, 9]. Formulations include gabapentin (also marketed as Neurontin, Gralise, or Horizant) and pregabalin (also marketed as Lyrica).

Per the US Food and Drug Administration (FDA), labeled indications for gabapentin include post-herpetic neuralgia and as adjunctive therapy in the treatment of partial seizures. The labeled indications for pregabalin include post-herpetic

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neuralgia, neuropathic pain from either diabetes or spinal cord injury, fibromyalgia, or as adjunctive therapy in the treatment of partial seizures [10, 11]. Increasingly, however, gabapentinoids (gabapentin and pregabalin) are being prescribed for off-label indications, with some studies estimating that off-label indications represent 95% of all cases [12]. These off-label indications include non-painful conditions such as social anxiety disorder, and of course painful conditions, with a decreased threshold for use in various acute and chronic pain conditions perhaps being the result of the Centers for Disease Control and Prevention (CDC) guidelines on opioid prescribing—which encourage clinicians to prescribe non-opioid analgesics [13]. That being said, even prior to the debut of the CDC guidelines on opioid prescribing, national prescribing data revealed that the number of gabapentin prescriptions dispensed from 2012 to 2016 increased from 39 million to 64 million [14]. Mirroring what has occurred in the outpatient arena, gabapentinoids have become common in the perioperative setting due to their perceived efficacy as a low-risk alternative to opioids and due to endorsements by expert panels and professional societies.

To date, many studies have examined the use of gabapentinoids in the perioperative setting. There is, however, much variability in these studies in terms of dose, frequency, duration, patient population, and outcomes. This article will review existing evidence on the efficacy of gabapentinoids in the perioperative setting as well as some adverse effects and controversies surrounding their use.

Efficacy of Perioperative Gabapentinoids for the Management of Acute Pain

A clinical practice guideline published in 2016 by the American Pain Society (APS), the American Society of Regional Anesthesia (ASRA) and an advisory group from the American Society of Anesthesiologists (ASA) strongly recommended, with moderate-quality evidence noted, that gabapentinoids be considered as a component of multimodal perioperative analgesia [15]. This guideline was preceded by multiple systematic reviews and meta-analyses on the use of gabapentinoids in the surgical patient [16–21]. These prior systematic reviews and meta-analyses included a study by Eipe et al. in 2015, which analyzed pregabalin as an adjunct for a variety of surgeries, ranging from major (orthopedic, thoracoabdominal, spinal, etc.) to less invasive (laparoscopic, e.g.). It was noted in this study that perioperative pregabalin caused a small reduction in pain in certain patients: a pooled mean reduction, with high quality of evidence, of 1.09 (95% CI, 1.8–0.37) for pain at rest and a pooled mean reduction, with moderate quality of evidence, of 0.94 (95% CI, 1.23–0.65) for pain with movement. Similarly, there was a small reduction in opioids: a mean reduction, with moderate quality of evidence, ranging from 9–21% (pooled ratio of means of 0.84, 85% CI, 0.78–0.91). The authors concluded that pregabalin could, in this setting, cause a small reduction of pain scores and opioid use, although the extent of benefit needs to be weighed against possible patient harm depending on the clinical scenario [22].

The American Pain Society (APS), ASRA, and the ASA 2016 practice guideline noted that existing evidence demonstrated a reduction in opioid requirement after a variety of surgeries as well as a reduction in pain scores. The surgeries for which the use of gabapentinoids was endorsed included thoracotomy, open laparotomy, total hip replacement, total know replacement, spinal fusion, cesarean delivery, and coronary artery bypass graft surgery, which on the whole are major and/or painful surgeries. Mentioned in this early consensus statement was also that the dose varied, with gabapentin ranging from 600–1200mg and pregabalin ranging from 100–300mg, with the timing of administration being either preoperative, postoperative, or both. The extent of expected opioid and pain reduction was not described for a given gabapentinoid regimen, although it was noted that higher doses might bring increased efficacy and sedation. In summary, it was noted that multimodal regimens are helpful in many perioperative scenarios, although the precise components will depend on the patient, surgical procedure, and setting. Reflecting some of the controversy surrounding gabapentinoids, the European Society of Regional Anesthesia does not broadly endorse the perioperative use of gabapentinoids [23].

A subsequent systematic review and meta-analysis in 2020 by Verret et al. pointed out the discrepancy between various professional societies recommendations regarding perioperative gabapentin use and aimed to incorporate new studies into an assessment of the benefit and risks of perioperative gabapentin use. The conclusion from this study was that there was not a *clinically meaningful* benefit of perioperative gabapentin use and that gabapentinoids should not be routinely administered to patients undergoing surgery [24]. This review included patients receiving either gabapentin or pregabalin before or after surgery; the total number of trials included was 281, representing 24,682 patients analyzed. Surgery types were 27% orthopedic or spinal, 23% non-endoscopic abdominal, 15% endoscopic abdominal, 10% ophthalmologic, ear–nose–throat, 7% plastic, peripheral vascular, breast, and others. Gabapentinoids were administered as a single dose in 68% of trials, preoperatively in 71% of trials, and both before and after surgery in 25% of trials. The primary outcome was postoperative pain intensity, with the analysis showing a small reduction of pain, which was not for all time points above a clinically significant difference of 10/100: mean difference reductions of pain were –10 at 6 hours (95% CI, –12 to –9), –9 at 12 hours (95% CI,

–10 to –7), –7 at 24 hours (95% CI, –8 to –6), and -3 at 48 hours (95% CI, –5 to –1). A secondary outcome was opioid administration, with the analysis showing a small reduction of opioid requirements: the mean difference in intravenous morphine equivalents was 7.9 mg (95% CI, –8.82–6.98, I^2 = 98%, 117 trials, 9,060 participants). A conclusion from this study was that additional trials were likely not required to show the impact of perioperative gabapentinoids on postoperative pain intensity.

The impact of gabapentinoids on other aspects of a patient's postoperative course, beyond the intensity of pain and amount of opioid consumed, has also been studied. Hah et al. in 2018 analyzed the effect of gabapentinoids on time to resolution of pain, indicated as five consecutive instances of 0 out of 10 pain, and a secondary outcome of time to cessation of opioid use, indicated as five consecutive instances of no opioid use. The patients in this study included those undergoing a variety of surgeries, ranging from total joint arthroplasty, thoracoscopic surgery, and mastectomy; the intervention was gabapentin 1200 mg preoperatively followed by 600mg three times daily versus an active placebo of lorazepam 0.5mg preoperatively followed by an inactive placebo, both for 3 days. The result was that gabapentin did not impact the time to cessation of pain (HR, 1.04; 95% CI 0.82–1.33; p = 0.73). There was, however, a 24% increase in the speed of postoperative opioid cessation in the gabapentin group (HR, 1.24, 95% CI, 1–1.54, p = 0.05). The median duration until opioid cessation occurred was 25 days in the gabapentin group and 32 days in the active placebo group. A conclusion from this study was that gabapentin might promote postoperative opioid cessation, but that additional information was needed to examine multi-day, postoperative gabapentin regimens [25].

An important clinical question related to the effect of perioperative gabapentinoids on postoperative pain intensity and opioid use is whether these medications play a role in the prevention of chronic postsurgical pain syndromes—either by reducing pain, reducing opioids, or some other mechanism. Chronic postsurgical pain (CPSP) is a state wherein acute postoperative pain is followed by a new chronic pain, lasting months to years after surgery. This phenomenon is more common after particularly painful surgeries, perhaps related in part to iatrogenic (and sometimes necessary) nerve damage—thoracic surgery, breast surgery, groin hernia repair, limb amputation, and coronary artery bypass surgery are common examples [26]. By some estimates, chronic postsurgical pain may occur in 10–50% of patients after surgery and be severe in 2–10% of cases [27]. The data on the role that gabapentinoids might play in the prevention of the development of CPSP are mixed. A Cochrane systematic review addressed this subject in 2013 [28]. Surgeries studied included joint arthroplasty, amputation, cardiac surgery, and others implicated in CPSP. Of the 10 gabapentin trials, 7 involved only a preoperative dose and 3 involved multi-day regimens ranging from 2 days to 30 days. Of the 5 pregabalin trials, the duration ranged from 1 day to 14 days. There was also considerable variation in the dose administered. A conclusion from the Cochrane review was that a meta-analysis did not show statistically significant reduction in pain compared to placebo at 3 or 6 months, although it was also noted that the results should be interpreted with caution, given the heterogeneity of the studies [28]. Another systematic review and meta-analysis on the subject by Clarke et al. in 2012 used a slightly different methodology, such as combining studies of gabapentin and pregabalin across different time points and pain assessment methods and also including different trials. This study did conclude that gabapentinoids could reduce the incidence of CPSP [29]. Subsequent studies have continued to be mixed. Another systematic review and meta-analysis in 2017 on the use of gabapentinoids after breast cancer surgery did not demonstrate an effect on the development of CPSP [30]. A subsequent randomized controlled trial of pregabalin given preoperatively and postoperatively for 2 weeks for patients undergoing cardiac surgery noted a lower incidence of CPSP [31]. Since virtually all of these studies concluded that there is a need for additional research to determine what role, if any, gabapentinoids might play in the prevention of acute pain, opioid use, and chronic pain.

Adverse and Harmful Effects of Gabapentinoids

The initial studies on perioperative gabapentinoids focused more on the statistically significant reduction in opioids and pain scores than side effects. It has been noted, however, that while gabapentinoids may bring a decrease in the incidence of postoperative nausea and vomiting and pruritis, perhaps due to an opioid-sparing effect, there is an associated increase in sedation, dizziness, and visual changes with their use [32]. Given the preponderance of the alpha$_2$-delta voltage-gated sodium channels to which gabapentinoids bind in the cerebellum and hippocampus, it is not surprising that these side effects, as well as ataxia and cognitive impairment may be present with their use [33]. While gabapentinoids have been added to many ERAS protocols, which have the goal of accelerated throughput through the perioperative system, the use of gabapentinoids has been implicated in an increased risk of respiratory depression during anesthesia recovery. This increased perioperative risk of respiratory depression, need for naloxone opioid reversal, and, at times, need for higher levels of care has been shown in patients receiving perioperative gabapentinoids when undergoing colorectal surgery, major laparoscopic surgery, joint arthroplasty, and other surgeries [34–37]. Potential pros

Table 1 Potential Pros and Cons of Perioperative use of Gabapentinoids

Pros	Cons
Part of multimodal analgesia regimen	Inpatient opioid use reduction is often clinically insignificant
Decreased inpatient opioid requirement	Dizziness, ataxia, and cognitive impairment may be increased
Decreased inpatient postoperative nausea and vomiting	Inpatient postoperative pain score decrease is often clinically insignificant
Decreased inpatient postoperative pain scores	Associated with an increased risk of respiratory depression, in particular if co-administered with opioids or if opioid use disorder is present
May result in faster cessation of opioids when prescribed postoperatively at higher doses	Potential for misuse and abuse

and cons of perioperative gabapentinoid use are summarized in Table 1.

The perioperative data linking gabapentinoids and respiratory depression mirror the data from the outpatient setting. By one account, the annual proportion of outpatient visits involving gabapentinoids increased almost fourfold from 2003 to 2016 (9.1 to 34.9 per 1,000 visits), with primary care providers representing almost half off all prescribers and nearly half of cases co-prescribed with opioids (32.9%) or benzodiazepines (15.3%). Almost all (96.6%) of the prescriptions were for off-label indications [38]. Other studies have indicated that patients prescribed both opioids and gabapentinoids had an increased risk of opioid-related death, with a stronger correlation when doses were moderate (900 – 1,799mg/day) or high (1,800mg/day or more) [39]. On this topic, the Food and Drug Administration (FDA) released a new warning: "Reports of gabapentinoid abuse alone, and with opioids, have emerged and there are serious consequences of this co-use, including respiratory depression and increased risk of opioid overdose death." This risk was noted also to be higher in patients with underlying respiratory disease, and that additional studies were needed to better quantify this risk and inform future guidelines on its use [40, 41].

There is also emerging evidence that gabapentin, originally thought to be a relatively benign, non-habit-forming medication, is increasingly being misused or abused. Pregabalin has previously been determined by the FDA to be a Drug Enforcement Administration (DEA) schedule V medication [42]. Increasingly, US States are classifying gabapentin as a controlled substance and requiring that gabapentin appears on state-run prescription drug monitoring programs [43, 44]. According to epidemiological and case report data from the USA, UK, Europe, India, and South Africa, gabapentin has been used for recreational purposes, to self-medicate other conditions, or in attempts at self-harm, with patients with co-existing other substance use disorders being at particular risk [45]. Self-medication of opioid-withdrawal symptoms or to heighten the euphoria associated with opioid use are among the possible reasons for recreational use. Ongoing systematic reviews and meta-analyses on this subject have illustrated that gabapentin misuse and abuse has resulted in increased hospital and emergency services utilization and opioid-related mortality, with patients at highest risk being those with comorbid opioid use disorder [46].

Conclusions

In the context of the opioid epidemic and the rise of enhanced recovery after surgery protocols [47–49], both of which prompt health care providers to administer non-opioid analgesics, gabapentinoids have increasingly been used for perioperative pain management. Studies have consistently demonstrated that gabapentinoids (gabapentin and pregabalin) administered perioperatively for a variety of surgeries can reduce pain scores and opioid consumption, although the extent of this reduction is generally statistically but often not clinically significant. These medications also result in lower levels of nausea, vomiting, and pruritis, perhaps as a function of being "opioid-sparing" interventions. The cost of these medications, however, includes an increased incidence of dizziness, ataxia, and cognitive dysfunction. There is also an increased risk of respiratory depression, both in the hospital and out of the hospital, in particular when gabapentinoids are paired with opioids, as is often the case. Recent studies have also shown that gabapentin and pregabalin are misused or abused in the outpatient world, particularly in patients with comorbid opioid use disorder. Certain patient populations, such as those of advanced age, underlying respiratory conditions, or those undergoing relatively minor or minimally painful procedures might not be ideal candidates for gabapentinoids. While some professional societies have in prior years provided endorsement of perioperative gabapentinoids as part of a multimodal regimen, there is far from consensus on their use. Increasingly, a patient- and procedure-specific approach is recommended, rather than just routine use of these medications for perioperative analgesia.

Compliance with Ethical Standards

Conflicts of Interests/Competing Interests Richard D. Urman reports unrelated funding and/or fees from Merck, Medtronic, AcelRx, Pfizer,

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Human and Animal Rights and Informed Consent Not applicable

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