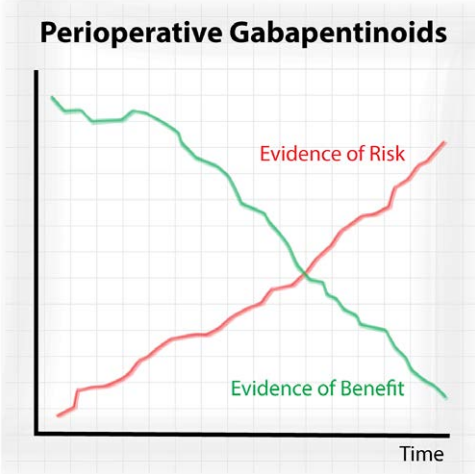
Perioperative Gabapentinoids

Deflating the Bubble

Evan D. Kharasch, M.D., Ph.D., J. David Clark, M.D., Ph.D., Sachin Kheterpal, M.D., M.B.A.

Prescription of gabapentin and pregabalin in the perioperative period has become increasingly common, if not *de rigueur*. These gabapentinoids have become ubiquitous components of protocols for early recovery after surgery and multimodal analgesia. Neither is approved by the U.S. Food and Drug Administration for preventing or treating surgical pain, but their use is predicated on widespread belief in their benefit, including pain reduction and opioid sparing, as well as their lack of side effects and risks. Nevertheless, these longstanding beliefs have recently been challenged.



"It is now clear that over the past two decades, evidence of benefit from routine perioperative administration of gabapentinoids has diminished, while evidence of harm has increased."

In this issue of Anesthesiology, Verret *et al.*[1] report a systematic review and meta-analysis of perioperative gabapentinoids for the management of postoperative acute pain. The analysis comprised 281 randomized clinical trials involving 24,682 adults, comparing gabapentinoids to placebo or another analgesic regimen or usual care, when initiated between 1 week before and 12 h after elective or emergent surgery under any type of anesthesia. The primary outcome was pain 6, 12, 24, 48, and 72 h after surgery. The results were statistically significant but clinically unimportant less postoperative pain at all primary time points (3 to 10% less), no difference in the proportion of patients achieving "appreciable" analgesia, no difference in subacute pain (postoperative weeks 4 to 12), and no effect on chronic postoperative pain (3 months or longer), for both gabapentin and pregabalin, regardless of when administered. Gabapentinoids were associated with statistically lower but clinically unimportant less postoperative opioid use (8 mg of morphine equivalent at 24 h). They were associated with less postoperative nausea and vomiting but more adverse effects, including dizziness and visual disturbances. The authors concluded that these data do not support the routine use of pregabalin or gabapentin for the management of postoperative pain in adults.

The article by Verret *et al.*[1] is commended to every practitioner who prescribes perioperative gabapentinoids and to those entrusted to author institutional protocols for early recovery after surgery or multimodal analgesia. The analysis was well executed, the number of patients robust, the quality of evidence properly evaluated, the results clearly presented, and the conclusions well supported and unambiguous. This article is entirely consistent with previous reports[2–6] but also brings forth additional information. The new analysis evaluated a broad surgical population, a long duration of outcomes, included additional trials, and, importantly, assessed minimally important clinical differences rather than just statistical differences.

We are then left to ask, how did we get here, and where should we go?

Evidence of Benefit

Gabapentin was approved by the Food and Drug Administration in 1993 for treatment of seizures and subsequently in 2002 for postherpetic neuralgia—the only pain indication. Pregabalin was Food and Drug

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Administration–approved in 2004 for neuropathic pain (diabetic neuropathy and postherpetic neuralgia), then fibromyalgia (2007), and spinal cord injury neuropathic pain (2012). Both drugs bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels in the spinal cord and peripheral nerves, decrease excitatory neurotransmitter release from activated nociceptors, inhibit ascending pain transmission, activate descending inhibitory pathways, and prevent hyperalgesia and central sensitization. They differ only in their pharmacokinetics. Neither drug is Food and Drug Administration–approved for treating or preventing surgical pain.

The early time course of perioperative gabapentinoid use was one of enthusiastic implementation. An early study used a single preoperative dose, evaluated patients for only 4 h postoperatively, and reported substantially (50%) less pain during movement and morphine consumption. An accompanying editorial heralded gabapentin as "a welcome addition to the anesthesiologist's pharmacopoeia of 'coanalgesics,'" and interest mushroomed. Within just a few years, numerous studies appeared, and preoperative gabapentinoids were celebrated as reducing pain scores, opioid requirements, and opioid-related side effects in the first 24 h after surgery with few adverse effects, deemed "promising," and perhaps the long sought after "protective premedication" or "preemptive analgesic." These remarkable effects were attributed to and "fit" with leading theories at the time, including prevention of central sensitization, inhibition of excitatory neurotransmitter release in the spinal cord, synergy with opioids, and prevention of opioid tolerance. What could be better? A groundswell of interest and exponential use of perioperative gabapentinoids ensued. They were evaluated for "preventive analgesia" and associated with moderate-to-large differences in chronic postsurgical pain. Enthusiasm for perioperative gabapentinoids swelled further, including higher doses, dosing earlier (day before surgery), and dosing longer (weeks) postoperatively. Perioperative gabapentinoid use was enthusiastically adopted, and became widespread and often routine.

In addition to the attractive and welcomed messages about benefits of perioperative gabapentinoids, the proliferation of routine use may relate to other factors, coincident events, and trends in anesthesia and surgical practice: (1) early published reports of gabapentinoid benefit were largely devoid of data on adverse effects and risk, and subsequent reviews had rosy descriptions of benefit or unsupported extrapolation; (2) the national epidemic of oral opioid overprescribing for chronic pain and accompanying addiction and overdose, prompting anesthesiologists and surgeons to seek alternatives to opioids; (3) an even more aggressive response by some anesthesiologists leading to a concept of "reducing or avoiding all perioperative opioids" (*i.e.*, "opioid-free anesthesia")[7,8]; (4) early recovery after surgery protocols, which initially recognized the influence of excess opioids on gut motility and recovery, and then in some cases evolved to a similar approach of "avoiding all opioids"; (5) adoption of "multimodal analgesia" as a concept but with uncritical widespread implementation of polypharmacy regimens whose clinical effectiveness and particularly adverse effect profile were insufficiently tested or evidenced[9]; (6) spillover of widespread gabapentinoid use for outpatient pain to perioperative use; (7) relatively small numbers of pharmacologic targets and drugs available for acute perioperative pain, juxtaposed with earnest practitioner desires to "do something"; and (8) professional society guidelines that recommend gabapentinoids.[10,11] Whether any aggressive or illegal pharmaceutical marketing of gabapentinoids (as had occurred earlier with Parke–Davis) influenced their perioperative use is not known.[6]

Recent years have seen a reversal of fortune for perioperative gabapentinoids, brought about by improved clinical research and its synthesis into informative and actionable evidence.[1–5] Compared with placebo, patients receiving perioperative gabapentinoids sometimes have pain and/or opioid consumption that is less, statistically, but small in magnitude (a few percentage points less pain and sparing only a few milligrams of opioid) and short-lived (often only a day) but not clinically meaningful and not preventing chronic postsurgical pain or opioid use.

Many placebo-controlled perioperative studies were designed to be single- or double-blinded, yet this is nearly impossible because gabapentinoids are sedating, and both patients and research staff may easily know who received active drug. Sedation alone might have a "placebo effect" with regard to pain. Indeed, in a seminal, well designed, and important investigation, an active placebo (lorazepam) was used instead of an inactive placebo, to truly blind patients and research staff. The result was that gabapentin did not affect either pain resolution or opioid cessation.[12] Thus with an active placebo, any evidence of gabapentin benefit evaporated.

Evidence of Risk

Clinical studies must evaluate both analgesia and all relevant side effects. Gabapentinoids have well described and frequent side effects. Because they bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, which are richly expressed in the cerebellum and hippocampus, they cause dizziness, balance disorders, ataxia, visual disturbances, sedation, somnolence, and cognitive impairment. Early gabapentinoid studies focused on analgesia but not side effects. In retrospect, however, there were early and clear yet underappreciated signals of side effects, most notably dizziness and sedation. Years later, it is now clear that perioperative gabapentinoids are associated with a greater risk of sedation, dizziness, and visual disturbances.[1–3] It is perhaps paradoxical that enhanced recovery protocols, which endeavor to avoid these very complications of sedation, somnolence, and cognitive impairment that can delay recovery, can advocate the routine use of gabapentinoids. More importantly, pregabalin use was associated with a nearly three-fold greater relative risk

of serious adverse events (life-threatening; resulting in death, disability, or significant loss of function; or causing hospital admission or prolonged hospitalization).[5] Day-of-surgery gabapentinoid use was associated with dose-dependent increased odds of postoperative pulmonary complications (respiratory failure, pneumonia, reintubation, pulmonary edema, noninvasive ventilation, or invasive mechanical ventilation) and intensive care unit admission and without decreased opioid requirements or length of stay.

Multimodal analgesia is predicated on favorable pharmacodynamic interactions whereby benefits of combination therapy exceeds the risks, either by synergistic analgesia but only additive toxicity or by additive analgesia with subadditive or diminished toxicity. Pregabalin plus opioids caused greater postoperative sedation, dizziness, visual disturbances, and confusion than opioids alone. Among the adverse effects of postoperative analgesics, the most dangerous is respiratory depression. Gabapentinoids, when combined with opioids, confer even greater respiratory risk than opioids alone. Pregabalin plus remifentanil caused additive analgesia but worse (potentiated) remifentanil ventilatory depression.[13] Perioperative gabapentinoid use was associated with greater postoperative respiratory depression, noninvasive ventilation, and naloxone use (as high as six-fold greater).[14,15] In a general population, concomitant gabapentinoid use substantially increases risks of opioid-related death.

It is now unmistakable that perioperative gabapentinoids have clinically significant adverse effects. Patient safety has emerged as a broader gabapentinoid concern. The Food and Drug Administration now recognizes and has issued warnings about adverse respiratory effects of gabapentinoids.[16,17] The Food and Drug Administration now requires updates to gabapentinoid labeling to include new warnings of potential respiratory depression and is requiring new clinical trials, particularly in combination with opioids, to assess respiratory depression.

Evidence and Action

It is now clear that over the past two decades, evidence of benefit from routine perioperative administration of gabapentinoids has diminished, while evidence of harm has increased. If any potential benefits exist in "special populations," published reports have yet to identify the benefits or the populations. Anesthesiologists and surgeons prescribe perioperative gabapentinoids because they believe they reduce acute postoperative pain, opioid use, and chronic postoperative pain. However, their expectations of meaningful clinical benefit are not supported. The conclusion reaffirmed by Verret *et al.* in this issue of Anesthesiology,[1] and reached by others before,[5,15] is that routine use of perioperative gabapentinoids for treatment of postoperative pain in adults is not supported. Furthermore, conducting even more clinical trials to evaluate analgesic benefits of gabapentinoids on acute postoperative pain is very unlikely to provide any new evidence.[1] The good intentions that led to routine gabapentinoid use should be redirected to lead the way out. The French Society of Anesthesia and Intensive Care Medicine now states that gabapentinoids should not be used systematically or in outpatient surgery.[18] Other societies should follow. As the weight of evidence has shifted and the risk–benefit balance tilted away from benefit, evidence-based practice impels revising if not eliminating the routine use of perioperative gabapentinoids in adults.

Key citations are included in this version. A version with full citations is provided as Supplemental Digital Content (http://links.lww.com/ALN/C399).

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Competing Interests

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Correspondence

Address correspondence to Dr. Kharasch: evan.kharasch@duke.edu

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