Electronic supplement

**Perioperative gabapentinoids: Deflating the bubble**

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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 multi-modal analgesia. Neither is approved by the US Food and Drug Administration (FDA) 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 lack of side effects and risks.1 Nevertheless, these longstanding beliefs have recently been challenged.

In this issue of Anesthesiology, Verret and colleagues report a systematic review and meta-analysis of perioperative gabapentinoids for the management of postoperative acute pain.2 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 hours after elective or emergent surgery under any type of anesthesia. The primary outcome was pain 6, 12, 24, 48, and 72 hours after surgery. The results were statistically significant but clinically unimportant less postoperative pain at all primary time points (3-10% less), no difference in the proportion of patients achieving ‘appreciable’ analgesia, no difference in subacute pain (postoperative weeks 4-12), 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 morphine equivalent at 24hr). 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 al2 is commended to every practitioner who prescribes perioperative gabapentinoids, and to those entrusted to author institutional protocols for early recovery after surgery or multi-modal 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,3-7 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 FDA in 1993 for treatment of seizures and subsequently in 2002 for postherpetic neuralgia - the only pain indication. Pregabalin was FDA-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 α2δ 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 FDA-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 hr postoperatively, and reported substantially (50%) less pain during movement and morphine consumption.8 An accompanying editorial heralded gabapentin as “a welcome addition to the anesthesiologist's pharmacopoeia of ‘coanalgesics’”,9 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 24hr after surgery with few adverse effects, deemed “promising”,10 and perhaps the long sought after “protective premedication”10 or “preemptive analgesic”.11,12 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.11 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.13 Enthusiasm for perioperative gabapentinoids swelled further, including higher doses, dosing earlier (day before surgery), and dosing longer (weeks) postoperatively.14 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,15 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”);16-18 4) Early recovery after surgery protocols, which initially recognized the influence of excess opioids on gut motility and recovery,19 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;20,21 6) Spillover of widespread gabapentinoid use for outpatient pain to perioperative use;22 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 which recommend gabapentinoids.23,24 Whether any aggressive or illegal pharmaceutical marketing of gabapentinoids (as had occurred earlier with Parke-Davis) influenced their perioperative use is not known.7

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.2-6,25 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 mg 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.26 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 α2δ 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.11 Years later, it is now clear that perioperative gabapentinoids are associated with a greater risk of sedation, dizziness, and visual disturbances.2-4 It is perhaps paradoxical that enhanced recovery protocols, which endeavor to avoid these very complications of sedation, somnolence, and cognitive impairment which can delay recovery,27 can advocate the routine use of gabapentinoids. More importantly, pregabalin use was associated with a nearly 3-fold greater relative risk of serious adverse events (life threatening; resulting in death, disability, or significant loss of function; causing hospital admission or prolonged hospitalization).6 Day of surgery gabapentinoid use was associated with dose-dependent increased odds of postoperative pulmonary complications (respiratory failure, pneumonia, reintubation, pulmonary edema, noninvasive ventilation, invasive mechanical ventilation) and ICU admission, and without decreased opioid requirements or length of stay.28

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 additive analgesia with sub-additive or diminished toxicity. Pregabalin plus opioids caused greater postoperative sedation, dizziness, visual disturbances, and confusion, than opioids alone.29,3,4 Among the adverse effects of postoperative analgesics, 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.30 Perioperative gabapentinoid use was associated with greater postoperative respiratory depression,31,32 noninvasive ventilation,33 and naloxone use (as high as 6-fold greater).33,34 In a general population, concomitant gabapentinoid use substantially increases risks of opioid-related death.35,36

It is now unmistakable that perioperative gabapentinoids have clinically significant adverse effects. Patient safety has emerged as a broader gabapentinoid concern. FDA now recognizes and has issued warnings about adverse respiratory effects of gabapentinoids.37,38 FDA 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.39 However their expectations of meaningful clinical benefit are not supported. The conclusion reaffirmed by Verret and colleagues in this issue of Anesthesiology,2 and reached by others before,6,25,33 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.2 The good intentions which led to routine gabapentinoid use should be redirected to lead the way out. The French Society of Anaesthesia and Intensive Care Medicine now states that gabapentinoids should not be used systematically, or in outpatient surgery.40 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.

**References**

1. Kharasch ED, Eisenach JC: Wherefore gabapentinoids? Was there rush too soon to judgement? Anesthesiology 2016;124:10-2

2. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard A-M, Leblanc G, Cossi M-J, Neveu X, Turgeon AF: Perioperative use of gabapentinoids for the management of postoperative acute pain: A systematic review and meta-analysis. Anesthesiology 2020

3. Eipe N, Penning J, Yazdi F, Mallick R, Turner L, Ahmadzai N, Ansari MT: Perioperative use of pregabalin for acute pain-a systematic review and meta-analysis. Pain 2015;156:1284-300

4. Mishriky BM, Waldron NH, Habib AS: Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth 2015;114:10-31

5. Fabritius ML, Wetterslev J, Mathiesen O, Dahl JB: Dose-related beneficial and harmful effects of gabapentin in postoperative pain management - post hoc analyses from a systematic review with meta-analyses and trial sequential analyses. J Pain Res 2017;10:2547-63

6. Fabritius ML, Strom C, Koyuncu S, Jaeger P, Petersen PL, Geisler A, Wetterslev J, Dahl JB, Mathiesen O: Benefit and harm of pregabalin in acute pain treatment: a systematic review with meta-analyses and trial sequential analyses. Br J Anaesth 2017;119:775-91

7. Goodman CW, Brett AS: A clinical overview of off-label use of gabapentinoid drugs. JAMA Intern Med 2019;179:695-701

8. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB: A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97:560-4

9. Gilron I: Is gabapentin a "broad-spectrum" analgesic? Anesthesiology 2002;97:537-9

10. Dahl JB, Mathiesen O, Moiniche S: 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004;48:1130-6

11. Ho KY, Gan TJ, Habib AS: Gabapentin and postoperative pain--a systematic review of randomized controlled trials. Pain 2006;126:91-101

12. Tiippana EM, Hamunen K, Kontinen VK, Kalso E: Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 2007;104:1545-56

13. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J: The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. Anesth Analg 2012;115:428-42

14. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR: Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology 2013;119:1215-21

15. Hoffer D, Smith SM, Parlow J, Allard R, Gilron I: Adverse event assessment and reporting in trials of newer treatments for post-operative pain. Acta Anaesthesiol Scand 2016;60:842-51

16. Kharasch ED, Avram MJ, Clark JD: Rational perioperative opioid management in the era of the opioid crisis. Anesthesiology 2020;132:603-5

17. Lirk P, Rathmell JP: Opioid-free anaesthesia: Con: it is too early to adopt opioid-free anaesthesia today. Eur J Anaesthesiol 2019;36:250-4

18. Wu CL, King AB, Geiger TM, Grant MC, Grocott MPW, Gupta R, Hah JM, Miller TE, Shaw AD, Gan TJ, Thacker JKM, Mythen MG, McEvoy MD: American Society for Enhanced Recovery and Perioperative Quality Initiative joint consensus statement on perioperative opioid minimization in opioid-naive patients. Anesth Analg 2019;129:567-77

19. Carmichael JC, Keller DS, Baldini G, Bordeianou L, Weiss E, Lee L, Boutros M, McClane J, Feldman LS, Steele SR: Clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Dis Colon Rectum 2017;60:761-84

20. Memtsoudis SG, Poeran J, Kehlet H: Enhanced recovery after surgery in the United States: From evidence-based practice to uncertain science? JAMA 2019;321:1049-50

21. Joshi GP, Kehlet H: Enhanced recovery pathways: Looking Into the future. Anesth Analg 2019;128:5-7

22. Yan PZ, Butler PM, Kurowski D, Perloff MD: Beyond neuropathic pain: gabapentin use in cancer pain and perioperative pain. Clin J Pain 2014;30:613-29

23. American Society of Anesthesiologists: Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists task force on acute pain management. Anesthesiology 2012;116:248-72

24. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL: Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016;17:131-57

25. Martinez V, Pichard X, Fletcher D: Perioperative pregabalin administration does not prevent chronic postoperative pain: systematic review with a meta-analysis of randomized trials. Pain 2017;158:775-83

26. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J, Efron B, Clay D, Sharifzadeh Y, Ruchelli G, Goodman S, Huddleston J, Maloney WJ, Dirbas FM, Shrager J, Costouros J, Curtin C, Carroll I: Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: A randomized clinical trial. JAMA Surg 2018;153:303-11

27. Ljungqvist O, Scott M, Fearon KC: Enhanced recovery after surgery: A review. JAMA Surg 2018;152:292-8

28. Ohnuma T, Raghunathan K, Moore S, Setoguchi S, Ellis AR, Fuller M, Whittle J, Pyati S, Bryan WE, Pepin MJ, Bartz RR, Haines KL, Krishnamoorthy V: Dose-dependent association of gabapentinoids with pulmonary complications after total hip and knee arthroplasties. J Bone Joint Surg Am 2020;102:221-9

29. Mathiesen O, Wetterslev J, Kontinen VK, Pommergaard HC, Nikolajsen L, Rosenberg J, Hansen MS, Hamunen K, Kjer JJ, Dahl JB: Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. Acta Anaesthesiol Scand 2014;58:1182-98

30. Myhre M, Diep LM, Stubhaug A: Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanil. Anesthesiology 2016;124:141-9

31. Weingarten TN, Jacob AK, Njathi CW, Wilson GA, Sprung J: Multimodal analgesic protocol and postanesthesia respiratory depression during phase I recovery after total joint arthroplasty. Reg Anesth Pain Med 2015;40:330-6

32. Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN: Multimodal analgesic therapy with gabapentin and its association with postoperative respiratory depression. Anesth Analg 2017;125:141-6

33. Ohnuma T, Krishnamoorthy V, Ellis AR, Yan R, Ray ND, Hsia HL, Pyati S, Stefan M, Bryan WE, Pepin MJ, Lindenauer PK, Bartz RR, Raghunathan K: Association between gabapentinoids on the day of colorectal surgery and adverse postoperative respiratory outcomes. Ann Surg 2019;270:e65–e7

34. Deljou A, Hedrick SJ, Portner ER, Schroeder DR, Hooten WM, Sprung J, Weingarten TN: Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. Br J Anaesth 2018;120:798-806

35. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W: Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med 2017;14:e1002396

36. Gomes T, Greaves S, van den Brink W, Antoniou T, Mamdani MM, Paterson JM, Martins D, Juurlink DN: Pregabalin and the risk for opioid-related death: A nested case-control study. Ann Intern Med 2018;169:732-4

37. FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression ([www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression](http://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression)), last accessed April 20, 2020.

38. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) ([www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin](http://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin)), last accessed April 20, 2020.

39. Martinez V, Carles M, Marret E, Beloeil H: Perioperative use of gabapentinoids in France. Mismatch between clinical practice and scientific evidence. Anaesth Crit Care Pain Med 2018;37:43-7

40 Aubrun F, Nouette-Gaulain K, Fletcher D, Belbachir A, Beloeil H, Carles M, Cuvillon P, Dadure C, Lebuffe G, Marret E, Martinez V, Olivier M, Sabourdin N, Zetlaoui P: Revision of expert panel's guidelines on postoperative pain management. Anaesth Crit Care Pain Med 2019;38:405-11