

Wherefore Gabapentinoids?

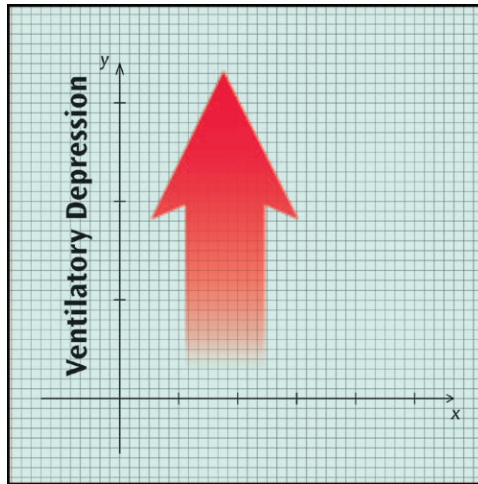
Was There Rush Too Soon to Judgment?

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NEARLY a quarter century ago, a group of Scandinavian investigators raised global awareness of the deadly risk of respiratory depression from a novel perioperative analgesic method: neuraxial morphine.¹ Postoperative respiratory depression from opioids remains a concern today, and in this month's issue of *ANESTHESIOLOGY*, a different group of Scandinavian investigators raises concern of a potentially dangerous drug interaction with application of multimodal analgesia.²

Multimodal approaches to perioperative pain are common in contemporary anesthesia practice. As posited by Kehlet and Dahl, "total or optimal pain relief cannot be achieved by a single drug or method or without significant side effects" and therefore they "recommend combined analgesic regimens (balanced analgesia) or a multimodal approach to the treatment of postoperative pain."³ As they further explained, the "rationale for this strategy is achievement of sufficient analgesia due to additive or synergistic effects between different analgesics, with concomitant reduction of side effects, due to resulting lower doses of analgesics and differences in side-effect profiles." Since then, a plethora of primary studies, reviews, and meta-analyses have evaluated innumerable combinations of drugs and techniques for multimodal analgesia, and these are often enthusiastically and variably implemented throughout clinical practice.⁴ American Society of Anesthesiologists Practice Guidelines for Acute Pain Management in the Perioperative Setting state that "whenever possible, anesthesiologists should use multimodal pain management therapy."⁵

The key question is how should practitioners assess all these drug combinations and the associated clinical studies



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and decide which combinations to implement clinically? One answer lies in evaluating the pharmacologic premise of combination therapies. Multimodal analgesia, conceptually and practically, rests almost exclusively on drug interactions that are pharmacodynamic (at the receptor or postreceptor level) not pharmacokinetic (changes in drug concentrations). Additivity occurs when the effect of two drugs together equals the sum of their individual effects, synergy occurs when the effect of two drugs together is greater than the sum of their effects when given alone, and potentiation occurs when one drug has no effect but increases the effect of another drug when given together.⁶ The goal of multimodal pain therapy is additive analgesia, with subadditive or diminished toxicity, or, synergistic analgesia with only additive toxicity. Clinical studies evaluating such drug combinations should evaluate both analgesia and all the relevant side effects.

Gabapentin and pregabalin block α -2- δ calcium channels in neurons. Gabapentinoids alone can reduce pain and are approved by the Food and Drug Administration for postherpetic neuralgia, diabetic neuropathy, and fibromyalgia in adults. American Society of Anesthesiologists Guidelines recommend that gabapentinoids should be considered as part of a postoperative multimodal pain management regimen.⁵ Oral gabapentinoids together with intravenous opioids may result in lower postoperative pain scores and reduced opioid consumption compared with intravenous opioids alone,^{5,7,8} although the magnitude of these effects varies considerably among studies, and the dose and duration of treatment needed to obtain them remain unclear.⁹ Reduction in nausea or vomiting by the combination is inconsistent.^{5,7}

Image: A. Johnson.

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Pregabalin alone causes major side effects, most commonly in cognition and coordination, including confusion, dizziness, somnolence, ataxia, disturbed attention, and thinking abnormalities.^{10,11} Pregabalin together with intravenous opioids causes greater postoperative side effects, including sedation, dizziness, visual disturbances, and confusion, than opioids alone.^{7,8,12} Thus, numerous clinical studies have studied the combination of gabapentinoids and opioids, evaluating mainly analgesia (pain, opioid sparing), but less so, or often not, the relevant side effects.¹² Hence, the true value of multimodal opioid–gabapentinoid regimens remains incompletely established.

This issue of *ANESTHESIOLOGY* reports the results of a clinical investigation by Myhre *et al.*² to address this very important issue. Their premise was that “to prove their utility in the perioperative period, the combination of opioids and gabapentinoids must demonstrate superior analgesia compared with either drug alone, and, furthermore, the combination should be beneficial compared with higher doses of opioid alone, and analgesic-related side effects should be reduced.” They performed a clinical study in healthy volunteers, to examine the effects of remifentanyl, pregabalin, and the combination, compared with placebo, on analgesia, ventilation, and cognitive function. The study used a crossover design, with each subject receiving all four treatments, and in randomized order, with enough time (washout) between treatment sessions to eliminate any carryover effects. Subjects received pregabalin (150 mg the night before and then again on the morning of the study day), a step-dose remifentanyl infusion targeting increasing concentrations of 0.6, 1.2, and 2.4 ng/ml for 40 min each and/or placebo(s) (for each drug). On every study day, pain, ventilation, and cognition were each assessed four times. Pain was measured using the standardized cold pressor test, with subjects holding their hand in 3°C water for a maximum of 2 min and then rating their pain on a visual analog scale (0 to 100). Ventilatory function was evaluated by spirometry, measuring respiratory rate, minute volume, and end-tidal carbon dioxide, with end-tidal carbon dioxide being the main ventilatory parameter. Cognition tests measured executive functions and sustained attention.

The analgesia results were entirely consistent with previous observations, but the side effect data were somewhat surprising, and the juxtaposition of positive effects and side effects is provocative. Remifentanyl alone caused dose-dependent analgesia, pregabalin alone caused mild analgesia, and the combination was *additive*. Remifentanyl alone caused dose-dependent ventilatory depression (increased end-tidal carbon dioxide and decreased respiratory rate and minute volume), and pregabalin alone had no significant effect, but the combination caused greater ventilator depression than remifentanyl alone; thus, pregabalin *potentiated* remifentanyl ventilatory depression. Cognitive performance was significantly reduced by the combination of pregabalin and remifentanyl but not consistently affected by either

drug alone. These data in volunteers are consistent with a recent retrospective review that demonstrated an approximately 50% increased risk of respiratory events in the post-anesthesia care unit in patients receiving more than 300 mg gabapentin preoperatively, a risk which was similar whether patients received general or neuraxial anesthesia.¹³

What are the clinical implications of the study by Myhre *et al.*? What is an acceptable incidence and magnitude of side effects to be paid for reduced pain and/or opioid consumption? An ideal multimodal drug combination causes greater analgesic effects and lesser side effects. In contrast, Myhre *et al.*² show that the combination of pregabalin and remifentanyl caused *additive* analgesia but *potentiated* ventilatory depression and caused *greater* unwanted cognitive side effects (greater analgesia but greater side effects). It is conceivable that the analgesic effects of pregabalin alone and manner of interaction with remifentanyl may differ in experimental nociceptive cold stimulation in healthy volunteers *versus* spontaneous and evoked neural activity occurring in patients sensitized after surgery. However, given ongoing concerns about postoperative ventilatory depression, particularly in the face of increasing prevalence of obstructive sleep apnea, as well as sedation, dizziness, and confusion, and the mixed picture of clinical effectiveness yet increased side effects when used in a multimodal regimen, available evidence to date suggests that the routine use of gabapentinoids in the perioperative period is yet not supported and perhaps not warranted. As in most questions of perioperative medicine, what we need are better data—what is the dose–response relationship of gabapentinoids for analgesia when combined with various opioids, and what is the relationship for adverse events from this combination, especially the risk of respiratory depression? The investigation by Myhre *et al.* is a great step in this direction.

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Competing Interests

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References

1. Gustafsson LL, Schildt B, Jacobsen K: Adverse effects of extradural and intrathecal opiates: Report of a nationwide survey in Sweden. *Br J Anaesth* 1982; 54:479–86
2. Myhre M, Diep LM, Stubhaug A: Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanyl. *ANESTHESIOLOGY* 2016; 124:141–9

3. Kehlet H, Dahl JB: The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. *Anesth Analg* 1993; 77:1048–56
4. Joshi GP, Schug SA, Kehlet H: Procedure-specific pain management and outcome strategies. *Best Pract Res Clin Anaesthesiol* 2014; 28:191–201
5. American Society of Anesthesiologists Task Force on Acute Pain Management: 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; 116:248–73
6. Raffa RB, Pergolizzi JV Jr, Tallarida RJ: The determination and application of fixed-dose analgesic combinations for treating multimodal pain. *J Pain* 2010; 11:701–9
7. 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
8. 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
9. Dahl JB, Nielsen RV, Wetterslev J, Nikolajsen L, Hamunen K, Kontinen VK, Hansen MS, Kjer JJ, Mathiesen O; Scandinavian Postoperative Pain Alliance (ScaPAlli): Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: A topical review. *Acta Anaesthesiol Scand* 2014; 58:1165–81
10. Salinsky M, Storzbach D, Munoz S: Cognitive effects of pregabalin in healthy volunteers: A double-blind, placebo-controlled trial. *Neurology* 2010; 74:755–61
11. Zaccara G, Gangemi P, Perucca P, Specchio L: The adverse event profile of pregabalin: A systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2011; 52:826–36
12. Mathiesen O, Wetterslev J, Kontinen VK, Pommergaard HC, Nikolajsen L, Rosenberg J, Hansen MS, Hamunen K, Kjer JJ, Dahl JB; Scandinavian Postoperative Pain Alliance (ScaPAlli): Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: A topical review. *Acta Anaesthesiol Scand* 2014; 58:1182–98
13. 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