Cognitive Effects of Perioperative Pregabalin: Comment

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To the Editor:

We read with interest the recent article by Myhre *et al.*[1] concerning the effects of pregabalin on cognitive function in the perioperative period. The authors note that there were significant changes in several components of the battery of tests, thus leaving the reader with the conclusion that pregabalin may cause significant detriment and demonstrably raise the risk of harm, including an increased risk of fall or behavior that would increase "risk of re-injury" (presumably wound dehiscence or other injury).[1]

As we routinely use nonopioid multimodal analgesia in our practice of perioperative pain management, we have several questions about this article and the data presented. First, was any reduction in dosage considered if the patient experienced side effects of the pregabalin? This is important as the patients were likely naïve to gabapentinoids and the dose utilized is the maximum dose that has been studied perioperatively (300 mg/day). Second, it would be helpful for the authors to note the test-retest reliability of this battery of tests and the correlation between them. The authors' conclusions suggested a significant risk, yet only two of the five tests showed any change from baseline and all of the tests were only administered once at each time point. Additionally, with approximately 20% of the patients in the control group not participating at 24 h due to pain or postoperative nausea and vomiting, could the authors comment on how stable their results would be if they assumed that these patients displayed poor function due to increased pain or an opioid effect? Third, it is unclear to the reader that a fraction of an error in two of the tests is a meaningful clinical difference at 3 to 5 days. What is the significance of 0.28 or 0.43 errors in actual practice? Finally, as the authors associate the change in executive function with an increased risk of fall in both the introduction and the discussion sections, it would be helpful for the reader to know whether this is speculative or if this event actually occurred in any patient.

Competing Interests

The authors declare no competing interests.

References

1. Myhre M, Jacobsen HB, Andersson S, Stubhaug A: Cognitive effects of perioperative pregabalin: Secondary exploratory analysis of a randomized placebo-controlled study. Anesthesiology 2019; 130:63–71

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Cognitive Effects of Perioperative Pregabalin: Reply

In Reply:

Drs. Allen and McEvoy have some very important comments and questions about our article[1] that we are happy to answer. We find that their input is valuable and relevant, and we thank them for their effort.

In their letter, they note that they routinely use nonopioid multimodal analgesia in their practice of perioperative pain management. We understand this, as pregabalin is part of that routine. One of our key messages is that pregabalin many places is used routinely perioperatively even if this is off-label use without proper documentation of efficacy and safety.[2] A quite recent editorial in Anesthesiology discussed this topic related to pregabalin in particular.[3]

Drs. Allen and McEvoy ask if any reduction in dosage of pregabalin was considered if the patient experienced side effects of pregabalin. They also comment that they believe the dose was high (300 mg/day).

The dose used is the recommended dose in several publications.[4,5] Our study differs from clinical practice, as it was a randomized and double-blinded trial, and individual titration of dose was not feasible. Of course, we had "stop rules," and possibility for unblinding in case of emergencies, but this was not needed except for one patient described in the flow chart who received only 450/600 mg pregabalin due to diplopia.[1] Besides, we think that dose reduction due to side effects is quite difficult

when patients are receiving multimodal treatment; which drug caused the side effect?

The battery of cognitive tests was carefully chosen to assess several different aspects of cognitive function. The Cambridge Neuropsychological Test Automated Battery tests are widely used by the pharmaceutical industry and clinicians to test effects of drugs on cognitive function. So-called "parallel tests" make sure retests are not identical (to avoid learning effects), yet comparable and reliable. We did not find it appropriate to readdress this carefully documented test system. The correlation between the tests was not a topic of interest since they test different aspects of cognitive function, and this was an exploratory analysis. The test battery used was quite extensive; most patients used 40 to 50 min each time, and thus repeated testing was not an option.

Drs. Allen and McEvoy find it questionable that 20% of the patients in the control group not were tested at 24 h due to pain or postoperative nausea and vomiting. We agree that this is a real weakness of our trial, and we have discussed this thoroughly in our article.

Drs. Allen and McEvoy also ask what a fraction of an error on day 3 to 5 really means clinically. Our attention has been on the effects on day 1 when patients took the drug. The tests 3 to 5 days after were done only to document whether day 1 changes had disappeared.

Yes, we speculate that the documented changes induced by pregabalin may affect motor control and may increase the risk of falls. There is extensive literature to document that the influences of motor and sensory impairments on falls are moderated by executive functioning. A number of studies suggest this.[6,7] We must admit we were not prepared on this issue, and did not register falls systematically. However, three patients, all three receiving pregabalin, had registered falls in their electronic patient journals. We did not mention this in our article since it was not a part of our preplanned systematic documentation of side effects.

The value and beauty of our study, and the need for exploratory analyses such as ours, are to aid future researchers to better document the effects of the intervention; first do no harm.[8]

Competing Interests

The authors declare no competing interests.

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References

1. Myhre M, Jacobsen HB, Andersson S, Stubhaug A: Cognitive effects of perioperative pregabalin: Secondary exploratory analysis of a randomized placebo-controlled study. Anesthesiology 2019; 130:63–71
2. Gupta SK, Nayak RP: Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities. J Pharmacol Pharmacother 2014; 5:88–92
3. Kharasch ED, Eisenach JC: Wherefore gabapentinoids? Was there rush too soon to judgment? Anesthesiology 2016; 124:10–2
4. 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
5. 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
6. Anstey KJ, Wood J, Kerr G, Caldwell H, Lord SR: Different cognitive profiles for single compared with recurrent fallers without dementia. Neuropsychology 2009; 23:500–8
7. Rapport LJ, Hanks RA, Millis SR, Deshpande SA: Executive functioning and predictors of falls in the rehabilitation setting. Arch Phys Med Rehabil 1998; 79:629–33
8. Hippocrates, Jones WHS, Potter P, Smith WD: Hippocrates: 2. Cambridge, Massachusetts, Harvard University Press, 1923

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Crystalloid/Colloid Renal and Disability Outcomes: Comment

To the Editor:

The recent article in Anesthesiology compared intraoperative fluid management by crystalloids *versus* colloids.[1] The authors analyzed postoperative sequelae 1 yr