Emerging Perspectives in Perioperative Use of Gabapentinoids

To the Editor:

We congratulate Schmidt *et al.*[1] for choosing a very appropriate topic at the forum of clinical concepts and commentary in Anesthesiology. The use of gabapentinoids as a component of multimodal approach toward postoperative pain management has recently been emerging as an area of interest for anesthesiologists. Published literature supports the authors' statement that perioperative use of gabapentinoids reduces pain after surgery and has opioid-sparing effects.

However, because of paucity of evidence, the authors were unable to clarify the role of gabapentinoids in chronic postsurgical pain. They concluded that the limited data that are available indicate some role of gabapentinoids in prevention of chronic postsurgical pain at the cost of increased sedation in the immediate postoperative period. We agree with the authors' view that there is a need of further studies to justify the effect of gabapentinoids on chronic postsurgical pain. At this juncture, it is pertinent to note that there is a significant abuse potential for these drugs, and a recent survey carried out in substance misuse clinics threw up a high proportion of respondents admitting to abusing gabapentinoids.[2] Therefore, while embarking on studies on long-term postoperative therapy to prevent chronic postsurgical pain, it is imperative to recognize this abuse potential be vigilant in identifying drug-seeking behavior and eventually formulate guidelines to prevent and treat such cases as and when they arise.

We agree with the authors' statement that the gabapentinoids are generally well tolerated. Even in cases of overdose or intoxication of gabapentinoids, only supportive care is usually sufficient and this is what makes them attractive to the clinician, but here we would like to emphasize that careful selection of patients is of utmost importance while using these drugs perioperatively as many patient factors such as age, renal dysfunction, type of surgery, and concomitant sedative use may predispose the patient to serious side effects. Indeed, even respiratory depression has been reported in the early postoperative period. The Ottawa Hospital Acute Pain Service has developed an algorithm to screen patients for risk factors (sleep deprivation, neuraxial opioid, renal dysfunction, neuraxial opioid use, obstructive sleep apnea, and elderly) before using pregabalin. Pregabalin is avoided in any patient found to have more than two risk factors, and in patients with one risk factor, it is recommended to prescribe pregabalin with caution.[3]

The authors have not discussed the role of gabapentinoids in regional anesthesia which has been highlighted in the recent literature. Recent studies have concluded that oral pregabalin in doses ranging from 75 to 150 mg is an effective adjuvant to spinal anesthesia[4] and patient-controlled epidural analgesia for total knee arthroplasty.[5] On the basis of published literature, it is evident that apart from pain relief and opioid-sparing action, gabapentinoids have other useful actions in the perioperative period which are recently being explored. Preoperative oral pregabalin reduces the incidence and severity of postdural puncture headache[6] and has also been shown to mitigate anxiety without increasing postanesthesia care unit stay in day-care procedures.[7]

The use of gabapentinoids is likely to witness an increase in the coming years. Therefore, the extensive review of the subject was interesting and well timed. We would once again like to congratulate the authors for their work.

Competing Interests

The authors declare no competing interests.

Veena Kachhwah, M.D., Zainab Ahmad, M.D. People's College of Medical Sciences and Research Center, Bhopal, Madhya Pradesh, India (V.K.). veenakachhwah_@hotmail.com; vkachhwah@rediffmail.com

References

1. 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
2. Baird CR, Fox P, Colvin LA: Gabapentinoid abuse in order to potentiate the effect of methadone: A survey among substance misusers. Eur Addict Res 2014; 20:115–8
3. Eipe N, Penning J: Postoperative respiratory depression with pregabalin: A case series and a preoperative decision algorithm. Pain Res Manag 2011; 16:353–6
4. Kohli M, Murali T, Gupta R, Khan P, Bogra J: Optimization of subarachanoid block by oral pregabalin for hysterectomy. J Anaesthesiol Clin Pharmacol 2011; 27:101–5
5. Jain P, Jolly A, Bholla V, Adatia S, Sood J: Evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee arthroplasty. Indian J Orthop 2012; 46:646–52
6. Rahmawy GEI, Rashwan D, Mohamed NN: The efficacy of preoperative pregabalin on reduction of the incidence and severity of postdural puncture headache after spinal anesthesia. Egypt J Anesth 2013; 29:357–61
7. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B: The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. J Psychopharmacol 2011; 25:249–53

(Accepted for publication April 10, 2014.)

In Reply:

We would like to thank Drs. van Schalkwyk and Kachhwah *et al.* for their comments concerning our article.[1] Dr. van Schalkwyk reports that our statement "gabapentinoids are very well tolerated" is "an assertion contradicted by even the most enthusiastic of the three old meta-analyses [we] cite." Our article cites five, not three, meta-analyses.[2–6] These were not old, but were the most recent meta-analyses on perioperative gabapentinoids available at the time of our writing the review, with two having been published in 2006 and the

remaining three in 2007, 2011, and 2012. The five meta-analyses we cited had mildly differing conclusions on the tolerability of gabapentin. One found "the incidence of gabapentin-related side effects (dizziness, lightheadedness, visual disturbance, and headache) was similar in the gabapentin and control groups."[5] Another found "gabapentin administration was associated with sedation and anxiolysis (OR = 3.28; CI, 1.21–8.87) but not associated with a difference in lightheadedness, dizziness, nausea, or vomiting."[3] Yet another found that gabapentin "increased the rates of dizziness and sedation in surgical patients" but "most of the reported dizziness episodes were mild and did not affect patient satisfaction."[4] A renewed search when writing this letter identifies only one more recent meta-analysis on perioperative gabapentinoids published in 2013, which fortunately specifically addresses how perioperative gabapentinoids were tolerated by patients. It states, as one of the three "Key Points," "both gabapentin and pregabalin were well tolerated."[7] Thus, the meta-analyses we cited and the additional new meta-analysis support that perioperative gabapentinoids are well tolerated. Although the focus of our article was not patient satisfaction, patient satisfaction is a key measure of how well perioperative gabapentinoids are tolerated, which becomes relevant in light of Dr. van Schalkwyk's concerns.

We identified nine trials in which perioperative gabapentin was assessed alone or in combination, in terms of its effect on overall patient satisfaction. One trial found no difference in satisfaction between gabapentin and control group, supporting that gabapentin is well tolerated,[8] whereas the remaining eight trials demonstrated statistically significant *improved* patient satisfaction when gabapentin was used. This suggests that regimens containing perioperative gabapentinoids may be better tolerated than standard higher opioid regimens.[9–16] Indeed, the study by Turan *et al.* examining the utility of supplementing perioperative epidural use with perioperative gabapentin explicitly states, "despite an increased incidence of dizziness [gabapentin] also increased patient satisfaction."[16] Similarly, of the four trials we identified that looked at patient satisfaction after perioperative pregabalin, two identified that patient satisfaction was similar in the presence or absence of pregabalin[17,18] and two found that pregabalin actually improved overall patient satisfaction.[19,20] In other words, although it is true that gabapentinoids have side effects, this is not an evidence for Dr. van Schalkwyk's suggestion that gabapentinoids are not well tolerated. In summary, the existing data suggest that patients tend to be more satisfied when gabapentinoids are used as part of a multimodal perioperative analgesic plan. Our statement that perioperative gabapentinoids are very well tolerated is both accurate and supported by the wealth of data accumulated on this issue.

Dr. van Schalkwyk also reports that we "fail to report accurately the findings of a more recent analysis." We regret he finds our characterization inaccurate. For the accuracy of the record, the referenced article states: "At least 50% pain relief over 6 hour was achieved by 15% with gabapentin 250 mg and 5% with placebo; giving a RB of 2.5 (95% CI 1.2 to 5.0) and an NNT of 11 (6.4 to 35). Significantly fewer participants needed rescue medication within 6 hours with gabapentin 250 mg than with placebo; NNT to prevent use 5.8."[21] In other words, even when given as a single postoperative dose at the bottom of the dose scale, gabapentin is superior to placebo, but is not as good as conventional stand-alone analgesics.

Finally, Dr. van Schalkwyk states "the overall tenor of the review is that gabapentin is substantially effective, both in the management of acute postoperative pain and in the prevention of chronic postsurgical pain. Neither contention is supported by independent analyses." He is correct about our tenor with regard to statements about the efficacy of gabapentin in acute postoperative pain, but not about whether these are supported by independent analyses. We do believe based on the large number of randomized clinical trials and the multiple independent analyses conducted as the meta-analyses cited above that perioperative gabapentin is substantially effective in reducing acute postoperative pain scores and opioid use in the first 24 h after surgery. Regarding this effect, our tenor has been correctly perceived. Furthermore, we think this is no longer substantially controversial.

Our tenor and opinion are more reserved for both the effect of pregabalin on acute pain and a postulated preventative effect of any gabapentinoid on chronic pain. Data are encouraging but less conclusive for pregabalin than gabapentin in the acute postoperative setting. With regard to effects on chronic pain, based on the existing literature and analyses, we do believe it "considerably more likely than not that gabapentinoids do have a preventative effect with regard to the formation of chronic postsurgical pain." We think that is different from asserting these drugs are substantially effective for this purpose.

Dr. Kachhwah *et al.* raise interesting and troubling points about two potential interactions of opioids and gabapentinoids that might generate clinical outcomes not often captured by perioperative analgesic studies of gabapentinoids: opioid abuse and respiratory depression.

We believe Anesthesiology and other journals in the field should encourage submission of follow-up articles documenting long-term follow-up from randomized controlled trials of perioperative gabapentinoids. Such studies should include not only chronic pain outcomes but also long-term opioid use outcomes. Long-term opioid use and/or misuse after surgery is an important clinical outcome with very significant public health implications deserving much more attention. The possibilities that perioperative gabapentinoids might reduce chronic opioid use and misuse after surgery by reducing early postoperative opioid use, or paradoxically might increase chronic opioid use and misuse by making opioids more rewarding, should be actively investigated.

Ultimately, more data are needed to know whether we should be avoiding gabapentinoids in people at high risk for

respiratory depression (*e.g.*, sleep deprivation, renal dysfunction, neuraxial opioid use, obstructive sleep apnea, and the elderly, as suggested by Kachhwah *et al.*), and caution is indeed warranted. However, the statement that pregabalin causes a predisposition to respiratory depression must be interpreted with caution. In the three case reports cited by Kachhwah *et al.*, all patients received perioperative opioids and all were successfully resuscitated as a result of naloxone administration. This suggests that too much opioid was a significant risk in these cases, but does not exclude the possibility that pregabalin might increase the risk of respiratory depression from coadministered opioids. Nonetheless, the high-risk population that Dr. Kachhwah *et al.* suggest not receive gabapentinoids is exactly the population most at risk from higher opioid doses used *in lieu* of gabapentinoids. It may ultimately be that these are the people who benefit most from perioperative gabapentinoids due to the opioid-sparing effects. We note that a small study reported elderly patients receiving perioperative gabapentin were less likely to experience postoperative delirium compared with patients who did not receive gabapentin—perhaps, as a result of the opioid-sparing effects of gabapentin.[22] Treatment of patients at increased risk of respiratory depression should be approached with the highest degree of caution with or without the use of perioperative gabapentinoids. Overall, until more data emerge we do support the approach advocated by Kachhwah *et al.* to screen high respiratory risk patients from routine use of perioperative gabapentinoids.

Competing Interests

The authors declare no competing interests.

Peter C. Schmidt, M.D., Gabriela Ruchelli, B.A., Sean C. Mackey, M.D., Ph.D., Ian R. Carroll, M.D., M.S.Epi.
Stanford University, Palo Alto, California (I.R.C.). irc39@pain.stanford.edu

References

1. 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
2. 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
3. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL: The analgesic effects of perioperative gabapentin on postoperative pain: A meta-analysis. Reg Anesth Pain Med 2006; 31:237–47
4. Peng PW, Wijeysundera DN, Li CC: Use of gabapentin for perioperative pain control—A meta-analysis. Pain Res Manag 2007; 12:85–92
5. Seib RK, Paul JE: Preoperative gabapentin for postoperative analgesia: A meta-analysis. Can J Anaesth 2006; 53:461–9
6. Zhang J, Ho KY, Wang Y: Efficacy of pregabalin in acute postoperative pain: A meta-analysis. Br J Anaesth 2011; 106:454–62
7. Yu L, Ran B, Li M, Shi Z: Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: A systematic review and meta-analysis. Spine (Phila Pa 1976) 2013; 38:1947–52
8. Gilron I, Orr E, Tu D, Mercer CD, Bond D: A randomized, double-blind, controlled trial of perioperative administration of gabapentin, meloxicam and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic cholecystectomy. Anesth Analg 2009; 108:623–30
9. Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y: Perioperative administration of gabapentin 1,200 mg day^{-1} and pregabalin 300 mg day^{-1} for pain following lumbar laminectomy and discectomy: A randomised, double-blinded, placebo-controlled study. Singapore Med J 2011; 52:883–9
10. Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC: Gabapentin improves postcesarean delivery pain management: A randomized, placebo-controlled trial. Anesth Analg 2011; 112:167–73
11. Tirault M, Foucan L, Debaene B, Frasca D, Lebrun T, Bernard JC, Sandefo I, Van Elstraete AC: Gabapentin premedication: Assessment of preoperative anxiolysis and postoperative patient satisfaction. Acta Anaesthesiol Belg 2010; 61:203–9
12. Sen H, Sizlan A, Yanarateş O, Senol MG, Inangil G, Sücüllü I, Ozkan S, Dağli G: The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol 2009; 26:772–6
13. Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G, Turan A: A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg 2009; 109:1645–50
14. Durmus M, Kadir But A, Saricicek V, Ilksen Toprak H, Ozcan Ersoy M: The post-operative analgesic effects of a combination of gabapentin and paracetamol in patients undergoing abdominal hysterectomy: A randomized clinical trial. Acta Anaesthesiol Scand 2007; 51:299–304
15. Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukçu Z, Yavuz E: Gabapentin: An alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006; 102:175–81
16. Turan A, Kaya G, Karamanlioglu B, Pamukçu Z, Apfel CC: Effect of oral gabapentin on postoperative epidural analgesia. Br J Anaesth 2006; 96:242–6
17. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I: Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. Obes Surg 2010; 20:1678–81
18. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K: Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 2008; 100:834–40
19. Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y: Perioperative administration of gabapentin 1,200 mg day^{-1} and pregabalin 300 mg day^{-1} for pain following lumbar laminectomy and discectomy: A randomised, double-blinded, placebo-controlled study. Singapore Med J 2011; 52:883–9
20. Ittichaikulthol W, Virankabutra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S: Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy: A randomized, double-blind trial. J Med Assoc Thai 2009; 92:1318–23
21. Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ: Single dose oral gabapentin for established acute postoperative pain in adults. Cochrane Database Syst Rev 2010: CD008183
22. Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, Ames C, Chou D, Weinstein P: Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology 2006; 67:1251–3

(Accepted for publication April 10, 2014.)