Pregabalin Effective for the Prevention of Chronic Postsurgical Pain: Really?

To the Editor

We have several comments regarding the recent article by Clarke et al.[1] reporting a systematic and meta-analysis of the properties of gabapentin and pregabalin in the prevention of chronic postsurgical pain. First, although the authors conducted an extensive search to identify relevant published studies, they have not included relevant studies appearing in www.clinicaltrials.gov. This site lists all IRB-approved protocols conducted in the United States and their associated results. It is important to note that this site identifies 3 phase III randomized, placebo-controlled multicenter trials designed by Pfizer assessing the properties of pregabalin in 3 different pain models: (1) 307 patients undergoing total knee replacement (150 mg [*n* = 103] and 300 mg [*n* = 100] versus placebo [*n* = 104]),[2] (2) 501patients undergoing total abdominal hysterectomy (150 mg [*n* = 162] and 300 mg [*n* = 170] versus placebo [*n*=169]),[3] and (3) 425 patients undergoing primary inguinal hernia repair (50 mg [*n* = 108], 150 mg [*n* = 106], and 300 mg [*n* = 103] versus placebo [*n* = 108]).[4] Thus, 852 of 1233 patients received pregabalin versus 175 in the Clarke et al.[1] report, and the effects of 3 dosing regimens (50 mg, 150 mg, and 300 mg) were assessed versus 2 (150 and 300 mg) in the Clarke et al.[1] report. Not one of these trials demonstrated any effectiveness of pregabalin during the acute and chronic phase.

Second, we question the value of a meta-analysis reporting the results of only 3 randomized trials containing a total of only 175 patients,[5–7] 69% of which were in 1 of the 3 studies.

Third, in this latter study, Buvanendran et al.[5] actually described the effects of celecoxib combined with pregabalin rather than on pregabalin alone. This is especially relevant considering that the 3 unpublished, randomized placebo-controlled trials[2–4] studying the effects of pregabalin alone failed to demonstrate any effectiveness of pregabalin.

The use of pregabalin for the perioperative management of pain and the prevention of chronic postsurgical pain is not currently approved by the Food and Drug Administration. On the basis of the negative data generated by Pfizer's phase III program, caution should be recommended when using pregabalin during the perioperative period, especially because the administration of 150 mg twice a day is often associated with significant sedation, especially in the elderly. This constitutes a significant limitation of the patient's functional recovery and increases the risk of perioperative falls.

Finally, nonreporting of these negative data recalls the classic article by Dickersin et al.[8] describing "existence of a publication bias of importance both to meta-analysis and the interpretation of statistically significant positive trials" ultimately leading to a requirement for registration of IRB-approved clinical trials such as those reported in this letter.[2–4]

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In Response

Our systematic review[1] was created as outlined in our search strategy by an experienced information specialist. The PRISMA guidelines published in 2009 do not endorse searching clinical trial registries.[2,3] Recently, the Methodological Expectations of Cochrane Intervention Reviews[4] has been updated with the following statement:

> Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible. Although ClinicalTrials.gov is included as one of the registers within the WHO ICTRP portal, it is recommended that both ClinicalTrials.gov and the ICTRP portal are searched separately due to additional features in ClinicalTrials.gov.

However, prompted by Dr. Chelly's comments[5] we have conducted an updated analysis using the ClinicalTrials.gov data to determine whether: (1) there is evidence of a publication bias and (2) the positive effects of pregabalin we reported are maintained. With the new data sets included from the 3 unpublished Pfizer pregabalin studies using participants that received 300 mg of pregabalin 3 months after surgery on the incidence of chronic postsurgical pain after total knee arthroplasty (22/59 pregabalin vs 27/61 placebo),[6] total abdominal hysterectomy (22/127 pregabalin vs 14/141 placebo),[7] and inguinal hernia repair (5/101 pregabalin vs 3/101 placebo),[8] the pooled odds ratio for the incidence of chronic postsurgical pain with the 5 pregabalin studies becomes an odds ratio 0.73 (0.28–1.89, $P = 0.51$). These new data question the positive pregabalin findings published to date with respect to the prevention of chronic postsurgical pain. We are supportive of the position that IRB-approved clinical trials should be registered and reported to ensure that publication bias is minimized when assessing clinical trials and meta-analyses. However, and in view of the fact that it is unlikely that the unpublished Pfizer data will ever become part of the peer-reviewed literature, it remains to be determined how data not undergoing the scrutiny of rigorous peer review should be weighed against published studies.

Our review article was written to examine the use of this class of medication in the perioperative setting for the prevention of chronic postsurgical pain based on the published literature available at that time. Studies evaluating the effectiveness of these agents in the acute and chronic postoperative pain settings continue to be published with mixed results.[9,10] It remains to be seen what the final verdict will be with respect to the benefits versus risks of these medications in the perioperative setting. Some institutions have adopted them routinely in a multimodal perioperative care pathway, whereas others have stepped away given the side-effect profiles of these medications. To that end, Dr. Chelly reiterates our cautionary note regarding the use of larger doses of the α-2-δ ligands given the increase in sedation and somnolence in the acute postoperative period seen most often in the elderly population and patients with compromised renal function.

Once again, given the limited number of studies identified in our review, the clinical heterogeneity of the trials identified, and the now documented evidence of a pregabalin publication bias,[2] future well-designed, appropriately powered studies are needed to clarify whether the α-2-δ calcium channel blockers have a role in the prevention of chronic postsurgical pain.

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