Author's response to reviews

Title: Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies

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Author's response to reviews: see over
Dear Editors,

On behalf of my coauthors, I am pleased to resubmit the manuscript entitled “Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies” for consideration for publication in *BMC Family Practice*. We have revised the manuscript to address the concerns of the reviewers. Revisions made to the manuscript are indicated in red text. Responses to the reviewers’ comments and a detailed list of revisions that were made to the manuscript are provided on the next page. Additionally, during revision of the manuscript we found errors in the calculations for rates of discontinuations owing to adverse events (Table 4) and have corrected those.

We hope these revisions address the concerns of the reviewers and that you find the revised manuscript acceptable for publication in *BMC Family Practice*.

Sincerely,

David Semel
Response to Reviewers’ Comments:

Reviewer #1:
The study by Semel et al. is an important contribution: the paper is well written, methodologically sound, analyses a unique data set, and addresses an important clinical question.

Discretionary Revisions

I have some suggestions that in my opinion would make this strong paper even stronger. The suggestions are Discretionary Revisions because the paper is already data rich and the suggested analyses may or may not be possible with the data in the authors’ database.

1) In addition to presenting the mean changes in pain and sleep interference scores by age and treatment groups, would it be possible to include data corresponding to the benchmarks for interpreting changes in chronic pain clinical trial outcomes as they were recommended by the IMMPACT group (Dworkin et al., J Pain. 2008 Feb;9(2):105-21.)? The IMMPACT group defined ‘moderately important’ and ‘substantial’ changes as a ≥ 30% decrease in pain scores and a ≥ 50% decrease, respectively. These levels of improvement also correspond to Patient Global Impression of Change levels of ‘much improved’ and ‘very much improved’, respectively. Do the available data allow calculation of the number of patients achieving IMMPACT benchmarks in the various treatment and age groups?

Authors’ response: We have updated the manuscript to include the requested outcomes of response rates for ≥30% decrease in pain, ≥50% decrease in pain, and endpoint pain score ≤3 to address the concerns of both reviewers. We have analyzed ≥30% and ≥50% pain relief response rates by both BOCF and LOCF methods of imputation, while response rates for pain score ≤3 at endpoint were analyzed only by LOCF because patients had to have baseline pain scores ≥4 to be included in these studies. A new table (Table 2) and descriptions of the methods and results of these analyses have been added to the manuscript (pages 7-11).

2) In addition to presenting data for individual adverse events, would it be possible to present data for the categories ‘number of patients with any adverse event’ and ‘number of patients with any serious adverse event’? This would allow ready comparison between pregabalin doses and age groups with regard to overall adverse events.

Authors’ response: These additional safety analyses are not within the scope of the current post hoc analyses. For each study, adverse event data are provided in the original published manuscript or online Web posting. In relation to safety data, during revision of the manuscript we found errors in the calculations for rates of discontinuation owing to adverse events (Table 4). These rates have been corrected and the results and discussion updated (pages 11, 12).

3) In the Methods section please provide references after this sentence ”Several of the studies excluded patients who had previously failed to respond to gabapentin at dosages #1200 mg/day for the treatment of DPN or PHN.“ It would be interesting to know how many of the studies used enriched enrolment.

Authors’ response: Six of the 11 studies excluded patients who had previously failed to respond to gabapentin. We have added this information
Reviewer #2

Firstly, let me say that I know personally a number of the authors, and respect their work. I know this work will have been done fastidiously, and it points to quite a large age effect for pregabalin in neuropathic pain. Unfortunately I have major reservations - not about how the analyses and calculations have been done, but what the target of the analyses were.

What we have here is situation in which the mean pain and sleep scores for each pregabalin dose are about the same at each age range. But the placebo scores fall with increasing age, suggesting a bigger effect with age. Which of course raises some interesting questions, the biggest of which is whether the observation is true, and secondly, even if true, whether it matters. Is it true? The problem here is the choice of mean data. The problem is that there is a huge skew in the distribution - with some patients getting a very large benefit in terms of pain and sleep reduction, while most others get very little if any. The average is where no-one is - as seen from the very large SDs, which are the same or larger than the mean values, and where +/- 2SDs covers almost all the scale. Using mean values like this would now not be acceptable to Cochrane pain or musculoskeletal groups, which have adopted the IMMPACT or PASS criteria. A recent IASP/Cochrane summary on systematic reviews in chronic pain makes the point (Pain doi:10.1016/j.pain.2010.05.011). Rather the choice is for dichotomised outcome of at least 50% or 30% pain relief, or patients with end of trial pain scores below 30/100 mm (or equivalent in other scales). These are outcomes with real clinical importance, and outcomes that patients themselves have told us that they want. Yet what we are given is an intense statistical approach that not more than 1 reader in 1000 would be able to fully comprehend. Most would give up, and probably rightly. But the dichotomised approach would probably also show that the proportion of patients with a good outcome, however defined, would be pretty consistent within pregablin dose and age group, but would fall with age with placebo. So any age difference is relative, not absolute. An interesting talking point, and given the long duration of chronic pain in most patients, and the very large negative impact on quality of life, one might put it down to increasing cynicism (or relaism) with experience. And that speaks to the question of whether it is true that there is more effect in older people. Clearly not, and the authors are very conservative in their language - saying only that there is just as big an effect in older people. But most readers will walk away with the impression of larger effect in Figure 3, showing the pregabalin minus placebo figures.

My advice would be to re-do the analysis with dichotomised outcomes, and ideally with the three outcomes of at least 30% pain reduction over baseline, at least 50% reduction over baseline, and pain at end of trial <30/100 mm. And with BOCF rather than LOCF analyses, since we know the overall discontinuation rate is not negligible. And with trials lasting 6 weeks or longer. With that analysis - as additional analyses, perhaps, with data in supplementary tables - the report would be very highly cited and of great clinical as well as academic value.

Authors’ response: We have updated the manuscript to include the requested outcomes of response rates for ≥30% decrease in pain, ≥50% decrease in pain, and endpoint pain score ≤3 to address the concerns of both reviewers. We have analyzed ≥30% and ≥50% pain relief response
rates by both BOCF and LOCF methods of imputation, while response rates for pain score ≤3 at endpoint were analyzed only by LOCF because patients had to have baseline pain scores ≥4 to be included in these studies. A new table (Table 2) and descriptions of the methods and results of these analyses have been added to the manuscript (pages 7-11).

The one other point one might make is that Table 1 should really include a breakdown of demographics by age group, as well as treatment group.

Authors’ response: Table 1 is already quite large and it would be difficult to add these additional data and keep this table in portrait format, which is the journal requirement for inclusion of tables integral to the manuscript. Thus, we would prefer to present the table as is. However, it should be pointed out that baseline mean pain and sleep interference scores are shown in Figure 1 broken down by both age and treatment group.