Reviewer’s report

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

Version: 2 Date: 20 July 2010

Reviewer: Andrew Moore

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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 a 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 pregabalin 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.

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.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have received research funds from Pfizer, and have been a speaker on Pfizer and Eli Lilly programmes discussing analyses in neuropathic pain.