Author's response to reviews

Title: A Cost-Consequences analysis of the effect of Pregabalin in the treatment of peripheral Neuropathic Pain in routine medical practice in Primary

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Author's response to reviews: see over
RESPONSE TO REVIEWERS

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A Cost-Consequences analysis of the effect of Pregabalin in the treatment of peripheral Neuropathic Pain under medical practice conditions in Primary Care settings.

Reviewer’s report #1
While I agree that a comparison of the outcome of specific treatments versus routine practice could be helpful in NeP, I feel that in the papers current format we cannot fully understand and so interpret the results.

• Major Compulsory Revisions
  1. The methods are not sufficiently clear to allow us to understand the cohorts. Without going into great depth we do need to understand how the study was conducted, in a stepwise fashion: how the physicians were selected; what population the patients were drawn from; at what stage patients came into the study etc. Otherwise the potential for bias is not clear.

  2. A large proportion of patients had PGB. Is this normal in Spain or is it due to the study design? If the second, how will this affect the results.

  3. Your comparator was prescribed a mixture of treatments, some considered appropriate for NeP and others not. You need to be able to justify this.

Changes introduced in new version of manuscript:

• Reviewer is right. Authors, following recommendation, have added a new paragraph in methods section and patient population subheading explaining the process of investigators and patient selection. The paragraph added is the following: “Sampling in the original study [26] was carried out by means of a stratified multistage probabilistic sample without replacement. The sampling frame was all health regions from the 17 autonomous communities of Spain. The first stage consisted of the selection of the PCS within each health region. The number of PCS to be selected in each region was proportional to the population of the region. The probability of selection of each clinic was related to the population of the area covered by the setting. In the second stage, one family physician or general practitioner per setting chosen at random within those with previous experience in clinical and epidemiological research was invited to participate. Those refusing to participate were replaced by others also selected at random in the same setting. The third stage consisted of the selection of patients. Patients were selected by a systematic sampling strategy from the daily list of all patients with an appointment with each of the participating physician meeting inclusion and exclusion criteria previously mentioned.”

• Again, reviewer is right. However, no changes have been included in the manuscript as a consequence of this comment. The reason is that the original study was carried out chronologically close to the availability of PGB in the country, particularly at the PCS level. Due to the fact that patient included were refractory to previous treatments, it is explicable that participant physicians chosen PGB as an alternative in many patients. The reviewer must taking into account that present manuscript included data from a secondary analysis which excluded patients previously treated with PGB.

• The reviewer is right. The two previous responses from authors try to also deal with this comment and with the differences in size of study groups. Due to the
You also need to be very clear about this in both your discussion and abstract. I was surprised that no TCAD/other AED than gabapentin was among those commonly used as a second line treatment. The non-PGB group was small so the inappropriately treated patients will make a great difference. A clearer methods section will help clarify how this happened.

4. You say the differences in baseline characteristics will bias results against PGB but the alternative cohort had more previous use of AEDs and TCADs so may include more refractory patients.

with the differences in size of study groups. Due to the observational design of the study, data presented here are important since they show how these types of patients are managed at PCS. The reviewer is right when he/she comment that many drugs used in these subjects are inappropriate. Authors considered that just one of the goodness of present study and its design is that show what is happening with such subjects in the real world, then, the paper may help readers and clinicians to improve their management of patients with chronic neuropathic pain. Regarding the specific comment on the use of gabapentin or TCAD, patients in the study received AE drugs other than gabapentin (ie; carbamazepine) or TCAD. We only described in the results section of patients those concomitant drugs given in % above 10% of patients. We now have added a sentence describing the rest of concomitant drugs used in the treatments of more than 3% of such patients. The new paragraph is as follows:

“Drug Treatment during the Study
Most patients of non-PGB group (67%) received two or more drugs [mean (SD): 2.2 (1.2), p=0.145 vs. pre-study number of drugs (table 3)], paracetamol being the most frequent (44% of subjects, mean dose: 2,144±1,010 mg/day), followed by gabapentin (33%; 1,288±543 mg/day), tramadol (29%; 214±130 mg/day), ibuprofen (19%; 1,438±517 mg/day), metamizol, an NSAID (17%; 1,679±606 mg/day), amitriptyline (10%; 37±35 mg/day), diclofenac (7%; 145±69 mg/day), codeine (5%; 10±8 mg/day) or ketorolac (5%; 18±17 mg/day). Drugs used by less than 3% of patients are not shown. The mean dose of the group receiving PGB monotherapy was 208±123 mg/day. The most frequently used drugs in the PGB add-on group (mean dose: 200±113 mg/day) were paracetamol (40%; 1,866±999 mg/day), tramadol (20%; 200±111 mg/day), metamizol (19%; 1,428±641 mg/day), ibuprofen (15%; 1,148±502 mg/day), diclofenac (10%; 111±45 mg/day), amitriptyline (6%; 46±29 mg/day), gabapentin (4%; 1,023±630 mg/day), ketorolac (3%; 14±14 mg/day) and codeine (3%; 93±86 mg/day). In this group, the mean number of drugs was 2.7 (1.0), p=0.159 (table 3).”

• No changes have been included in the manuscript as a consequence of this comment. While the reviewer is right that a few more patients were treated previously with AEDs in the non PGB group which could say that more refractory patients were included in such group (being the difference of hardly statistical significance; p=0.043), TCAD use was similar among groups (without statistically significant differences). Nevertheless, when we said that baseline results could bias again PGB; this was included as a possible limitation of the paper rather than an argument in favor of PGB. In addition, pain intensity, LWDE or numbers of non-scheduled medical visits at baseline were clearly worst in subjects who were chosen to be
5. Table 5 reports within treatment comparison of baseline and change to follow-up for a range of costs, including secondary care and tests. As most of the patient investigations are completed around the time of diagnosis do the p-values tell us anything? Patients had to have six months history of pain but they may not have consulted for this period or investigations may have taken some weeks.

6. The paper reports that the PGB cohorts had significantly greater cost reductions. They did, but this appears to be due to greater pre-PGB costs rather than lower costs post-treatment. Both comparisons should be provided. This should be discussed. Does this difference in pre-treatment cost suggest some residual bias? Could there be differences in health care coverage?

7. The methods state that significant results were adjusted but the tables only have one value. Which is it? What covariates were included in the model? It is normal to adjust all appropriate comparisons as non-significant results can become significant! Therefore all comparisons of change in pain and cost should be adjusted with both results reported.

8. The three NeP conditions included have very different short-term prognoses. Can they be looked at separately? If not this needs to be discussed.

Minor Essential Revisions

- No changes have been included in the manuscript as a consequence of this comment. The reviewer is right. However, in case of refractoriness many GPs may want to explore additional reasons for patient non response to therapy. For example, they may request or sign new complementary test or new scans when patients came back to the physician without pain reduction in the last 6 months.

- Differences in care coverage could not happened as the Spanish NHS is rather homogeneous in term of care offered to patients, particularly type of drugs, medical services, tests, etc. The greater cost reductions showed in PGB groups were adjusted by baseline values, since these were different and then a comparison of cost at the end-of-trial visit only could not be appropriated from a statistical point of view without adjusting by baseline differences. Neither a comparison of the observed change without adjusting by the baseline values. Authors think that the most important is to show the change during the trial which may be possibly imputed to the treatment used in any particular cohort. To show if differences exist at the end-of-trial visit has no value taking into account that differences already were observed in the baseline visit.

- In the methods section, Statistical analysis subheading, we report of the type of possible confounding variable included in the ANCOVA models. These covariates were the baseline values and the number of previous drugs in any comparison. Again, the values included in tables are adjusted changes. We have added the following footnote in tables 3, 4 and 5 in order to gain clarity: “Between groups changes comparison adjusted by baseline values and number of previous drugs.”

- The analysis was carried out in one group only. Just including the main reasons for NeP in one-group only. The reviewer is right since prognoses of these conditions are different. However, the trial, and its conclusions, is related to the 12-weeks study period only, that cover perfectly the short-term evolution of such three causes of NeP. Nevertheless, we have included this as a possible limitation in the discussion. We have added the following sentence in the limitations section of manuscript: “Finally, the etiological diagnosis of types of NeP included here may have different long-term evolutions both in term of outcomes follow-up and health resources utilization and corresponding costs. Due this, any findings observed in this research should be limited to the trial duration of this study.” We also, added the sentence “during the 12-week period of the study.”, in the conclusion section of manuscript and in the abstract.
9. The results are repeated in the discussion on a number of occasions, they should be removed. Similarly the objective is stated both in the introduction and methods. Figure 2 would be improved by a clear title.

- No changes have been included in the manuscript as a consequence of this comment. The idea of repeating some results is to emphasize the importance of some findings of this study or to explain the findings. For the same reason, the repetition of the objective in the methods section was made to clarify the groups compared and outcomes analyzed.

- The manuscript has been reviewed for any grammatical mistake or error.

**Reviewer #2**

1. Is the question posed by the authors well defined?
   Yes
2. Are the methods appropriate and well described?
   Yes
3. Are the data sound?
   Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Yes
6. Are limitations of the work clearly stated?
   No – there are some clarifications to be made.
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   Yes
8. Do the title and abstract accurately convey what has been found?
   Yes
9. Is the writing acceptable?
   For the most part – there are still some errors requiring repair

The below represent Major Compulsory Revisions Suggestions:

**Abstract**

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“Methods: PCS included subjects above” should be “Methods: Subjects from PCS were older than”

**Introduction**

“All of this influencing the” should be “All of this influences the”

“alpha2-delta ligand that displays analgesic” should be “alpha2-delta ligand of voltage gated calcium channels that displays analgesic”

“naturalistic” should be “real world”

**Methods**

How was the decision made to use PGB or not to use PGB for each subject?

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- Many thanks. We have repaired as many grammatical mistakes as possible in the text.

- Many thanks. All these sentences have been corrected.

- In methods section, the following paragraph was included in the original version of manuscript
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who paid for the PGB or non-PGB for each subject?</td>
<td>included in the original version of manuscript explaining how the decision of using or not using PGB was made: “The study was non-interventional, and the analgesic treatment prescribed was determined by the clinical judgment of physicians. Doctors could substitute the previous treatment by one or several other drugs, or add a new drug to the existing therapy.”</td>
<td></td>
</tr>
<tr>
<td>What is the LIDO Study?</td>
<td>- The study was designed as non interventional, trying to capture the real word. As a consequence, treatments were not provided to patients, and they were paid by the NHS or the patients by them-self, depending of patient’s social security status.</td>
<td></td>
</tr>
<tr>
<td>Why was a blinded study not performed? Were there particular reasons for this?</td>
<td>- The results included in this work is a secondary analysis of data extracted from the LIDO study; a prospective cost-of-illness study in subjects with peripheral Neuropathic pain.</td>
<td></td>
</tr>
<tr>
<td>The measurement of % of labour disability is extremely subjective and has limitations which need to be discussed.</td>
<td>- The study was designed as an observational, non intervention real world study. As a consequence, the objective of the study was to capture how NeP patients are managed in daily routine medical practice. Any blinding or dummy measurement would have incorporated interferences or bias in the results obtained during the study.</td>
<td></td>
</tr>
<tr>
<td>What survey tool was used to capture health care resource utilization?</td>
<td>- The reviewer is right. We have added this as a limitation. The following sentence was included in the limitation section of manuscript: “To calculate LWDE, the study recorded patient’s self-perceived productivity, which could incorporate some degree of bias or uncertainty.”</td>
<td></td>
</tr>
<tr>
<td>Was the analysis performed by Pfizer or was this at arm’s length?</td>
<td>- We used a questionnaire designed ad hoc for this trial.</td>
<td></td>
</tr>
<tr>
<td>With such a large percentage of patients not working, how reliable is the use of work-related cost measurements?</td>
<td>- The analysis was performed by a C.R.O. engaged specifically for this trial.</td>
<td></td>
</tr>
<tr>
<td>What is metamizol? I realize that this is an NSAID, but many British and North American readers will not recognize this.</td>
<td>- Authors, however, believe that as this was a real world study including a large sample of patients, the trial was able to show how is the impact of peripheral NeP in different aspects of health resources utilization and impact on work activity. This study also showed that the indirect component of cost of neuropathic pain is the most important component of the cost-of this illness.</td>
<td></td>
</tr>
<tr>
<td>Discussion</td>
<td>- Metamizol is a non narcotic analgesic which belongs to NSAID group. We have added a footnote in table 2 clarifying this for readers and in results section when metamizol is cited for the first time.</td>
<td></td>
</tr>
<tr>
<td>“capture out-of pocket cost” should be “capture out-of pocket cost”</td>
<td>- Many thanks. It has been corrected.</td>
<td></td>
</tr>
</tbody>
</table>
**Table 1**
How was the cost per lost-workday arrived at? What typical daily salary was used to derive this? Did this use white collar and blue collar incomes?

**Table 2**
P2 looks like p squared rather than p with a reference number – please modify

What were the non-PGB treatments used? This is not clarified in any location in terms of frequency of use.

- As mentioned in section methods, we used average national wages per worker and per month divided by 30 days. This included any type of incomes irrespective of working segment and it is given by the National Institutes of Statistics. We now have specified in new version of manuscript that wages are national average.

- This has been corrected changing numerical symbols in all tables to avoid confusing.

- This information is included in section results, subheading “Drug treatment during the study”

- The manuscript has been reviewed for any grammatical mistake or error.
Reviewer #3

The study by Navarro et al, performs the cost-effectiveness analysis of the pharmacological effects of pregabalin in the treatment of peripheral neuropathic pain. The authors argued that the importance of this study consists on the fact that it has been performed in a “real clinical sample”. I agree with the assumption of the authors that clinical trials are not completely representative of what happen in the “real world” and that we need of pharmacological studies able to obtained data more typical of what we observe in clinical practice. Although this study represents an attempt to achieve these data, the current version of the paper has some shortcomings from both clinical, pharmacological and methodological point of view that have to be revised and clarified before publication.

• We thanks reviewer for his/her comments. However, authors really do not know exactly how to response properly. We would thank reviewer were able to be a little bit more precise or specific with changes or modifications to be included in the manuscript. We would very much appreciate to have some details on why to deal with the shortcomings on clinical, pharmacological and methodological aspects of study.