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

Authors:

Ana Navarro (navarrosiguero@eresmas.com)
María T Saldaña (zatosaldana@yahoo.es)
Concepción Pérez (cperez.hlpr@salud.madrid.org)
Sandra Torrades (sandra.torrades@ebi2005.com)
Javier Rejas (marina.desalas@pfizer.com)

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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.

<table>
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<th>Reviewer’s report #1</th>
<th>Changes introduced in new version of manuscript</th>
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<td>The additional description of the sampling in the methods is helpful but I suggest a more step-wise report of what was completed would make things clearer for the reader with the sampling near the beginning of the methods. This description of sampling together with the inclusion criteria indicate that in fact few patients use other treatments in the absence of pain reduction after treatment with at least one course of an analgesic drug in monotherapy.</td>
<td>• The section description sampling process has been moved at the beginning of subsection “Study sample” and also some clarifications (in yellow) have been added in sampling description section in order to gain in clarity. The sampling paragraph remains now as follows:</td>
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<td>The finding that most of the comparator group was not on appropriate treatment needs to be discussed. To be clear, the issue of non-appropriate treatment in the control group should be mentioned in the abstract conclusion.</td>
<td>“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 PCS list was obtained from the catalogue of health centres of the Spanish Ministry of Health and the density of population from the National Institute of Statistics. The probability of selection of each clinic was related to the population of the area covered by the setting. A random process was applied to chose centers in each region. In the second stage, the center was contacted by phone in order to get a list of possible investigators considered candidate for participation in the study. Then, a 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. Every physician was responsible for selecting patients for the study, and was told to choose consecutive subjects (systematic sampling strategy) from the daily list of all patients with an appointment with each of the participating physician meeting inclusion and exclusion criteria mentioned below.</td>
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<td></td>
<td>• We have added the following sentence in the conclusion of abstract: “The use of non-appropriate analgesic therapies for neuropathic pain in a portion of subjects in non-PGB group could explain partially such findings.”</td>
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There are major differences in terms of baseline characteristics and costs. Given the observational nature of the data, the discussion needs to fully address these differences and the risk of residual confounding.

• We have rewritten some parts of the limitation section of manuscript in order to address baseline differences. The section remains now as follows: “Our study presents, however, some limitations that should be borne in mind. Among them, the observational design of the study implies potential confounding factors. One of these factors is confounding by indication, inherent to observational studies involving drugs [44]. This would explain, for instance, the significant differences observed among the three groups selected for the analysis of their baseline clinical characteristics, use of complementary tests, mean number of medical visits, particularly to primary care and specialist visits, as well as LWDE. However, these differences would be expected to bias the results against PGB since, as these patients had higher levels of baseline pain severity, significantly more LWDEs, more prescribed complementary tests, or more medical visits, yielding to higher quarterly costs in cohort receiving PGB as an add-on therapy. Then, certain risk for residual confounding could not be ruled out. In the PGB monotherapy group, this might be explained by a lower use of drugs in previous therapeutic schedules, or to a lower use of opioids before the study, compared to higher levels of previous exposure to NSAIDs and paracetamol in the other two groups. In general, subjects receiving PGB in monotherapy were exposed to lower percentages of analgesics, except tricyclic drugs, than the other two study groups. On the opposite, patients in the PGB add-on group received lower levels of exposure to antiepileptic drugs. These could be the only explanation for mentioned baseline differences, as groups were similar in distribution of type of neuropathic pain, elapsed time from diagnosis and the rest of demographic characteristics collected in the trial. It appeared that subjects receiving PGB as monotherapy could be less resistant patients. Other possible limitation is the unbalanced sample size of non-PGB group in comparison with the other two groups reflecting a possible selection preference of participants for pregabalin. However, and as mentioned, bias could go against pregabalin given the worst profile of subjects in some variables and the statistical analysis performed dealt with this unbalanced sample size of groups. Another limitation is that the study was not able to capture out-of-pocket cost, thus, a full societal perspective economic evaluation could not be performed. However, the economic impact of this limitation on overall costs is really limited due to the nature of NeP as most direct healthcare resources consumption are financed by Social Security and indirect costs represent the largest portion of total cost in these conditions. Also, it is worthy to comment on the diagnosis of NeP in the study. While patients were identified using ICD-10 classification criteria for peripheral NeP in conjunction with a diagnostic tool administered to assist general practitioners in categorizing the neuropathic component of pain, we cannot exclude the possibility of misdiagnosis to some extent. On the other
hand, to calculate LWDE, the study recorded patient’s self-perceived productivity, which could incorporate some degree of bias or uncertainty. Finally, the etiological diagnosis of types of NeP included here may have different long-term evolutions both in terms of outcomes follow-up and health resources utilization and corresponding costs. Due to this, any findings observed in this research should be limited to the trial duration of this study.

Patients in non-PGB and PGB add-on therapy groups were receiving analgesics without indication for neuropathic pain, such as paracetamol, metamizol or NSAIDs to some extent. The use of these non-appropriate therapies could explain partially the lower effectiveness and higher resources utilization observed in the results of non-PGB group; even they were treated with appropriate therapies in at least three out of four cases (near 77% of subjects in this group were treated with gabapentin, tramadol, codeine or amitriptyline, perhaps at doses in the lower end of its therapeutic range). On the opposite, all subjects included in PGB groups received an appropriate analgesic (an analgesic indicated for the treatment of neuropathic pain) by definition.

Overall, despite these limitations and the fact that a residual confounding can not be completely ruled out, the results of this analysis complement the findings observed with PGB in clinical trials, then consolidating PGB as an effective therapy for the treatment of peripheral NeP due to diabetic neuropathy, postherpetic neuralgia or trigeminal neuralgia in real world conditions of care. This effectiveness resulted in a reduction of the use of direct healthcare and indirect resources in routine medical practice, leading to lower costs both for the National Health System and society. Other learning from this trial was the observation of inadequate use, type and/or doses, of analgesics for neuropathic pain conditions in the real world in an important proportion of subjects.

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

- No changes
- No changes
- No changes
- No changes
- No changes
6. Are limitations of the work clearly stated?
Not in all cases - there are still important points not described in the text which require addition

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- No changes

- We have added the following sentence in the conclusion of abstract: “The use of non-appropriate analgesic therapies for neuropathic pain in a portion of subjects in non-PGB group could explain partially such findings.”

- No changes

- The section Study Design has been modified in order to increase the level of description of the original study. However, the methods section of the manuscript is describing the entire design, variables and measurements included in the original study that was the source for the secondary analysis presented in current manuscript:

The below represent Major Compulsory Revisions
The LIDO Study needs to be described and referenced in more detail.
The survey tool used to capture health care resource utilization needs to be provided in an appendix for readers to view.

Study Design

The results of a secondary analysis of a multicentre, observational and prospective 12-week study (LIDO study)\[26\] are presented. The LIDO study was designed with the objective of determining the prospective cost-of-illness of treating refractory NeP patients in real life conditions in PC settings in Spain. Also, patient’s health status, disability, quality of life, sleep disturbances and symptoms associated with neuropathic pain in addition to pain measurements were assessed at baseline and after 12-weeks of follow-up. The study was carried out between September 2005 and April 2006, and 391 PCPs representative of the entire Spanish territory participated. Due to the non-interventional design of the study, only two visits (baseline and 12-weeks visit) were scheduled within the frame of the study. The analgesic treatment prescribed was determined by the clinical judgment of physicians, as the protocol did not establish any particular therapy. Doctors could substitute the previous treatment by one or several other drugs, or add a new drug to the existing therapy as duly appropriated. Study sampling and patients’ selection requirements are described below in this section. In the LIDO study, healthcare resources utilization, along with the number of sick leaves and productivity while working in active population and patient-reported-outcomes variables were collected for a 3-months time frame and are described below. The study was approved by the Ethics Committee of Clinical Research of the Hospital de la Princesa (Madrid).

The objective of this secondary analysis was to compare the effect on pain alleviation of two PGB regimes; add-on and monotherapy (PGB add-on and PGB monotherapy groups), with a therapeutic regime for NeP not including PGB (non-PGB group). The impact of such therapies on healthcare and non healthcare resources utilization and its corresponding costs was also analyzed.

The reference for LIDO study has been updated with the following:


- There was no specific tool to capture health care resource utilization needs. A Case Record Form with fifteen pages was designed specifically for the study, along with a patient diary collecting pain intensity and health status on a weekly basis. On the CRF, pages were designed to collect utilization of every type of health resources collected from the medical records of the patient or directly from him/her by means of a face to face interview. The CRF is annexed in an appendix to the manuscript as per requested by reviewer.
Mention of the company performing the analysis needs to be listed in the paper.

- The following sentence has been added at the beginning of Statistical Analysis section of manuscript:
  
  *Statistical analysis was performed by European Biometric Institute (EBI), at Barcelona, an independent body engaged by the sponsor of the study.*