Author's response to reviews

Title: Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: A systematic review

Authors:

Melanie Chapman (Melanie.Plested@heronhealth.com)
Sangeeta Budhia (Sangeeta.Budhia@heronhealth.com)
Zahava Gabriel (Zahava.Gabriel@pfizer.com)

Version: 3 Date: 16 July 2010

Author's response to reviews: see over
Dear Editors

**RE: MS: 1379144351328959**
Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: A systematic review

Melanie Plested, Sangeeta Budhia, Zahava Gabriel

Many thanks for the referee comments on the manuscript that was submitted for consideration to be published as an original article in BMC Neurology. Please see responses to specific comments by each of the three reviewers. Where possible and relevant we have sought to address these comments. As a result there have been some minor modifications to the manuscript which are highlighted in yellow.

Thank you again for the feedback. I trust the responses and modifications to the manuscript address the comments to your satisfaction.

Yours sincerely

Melanie Plested on behalf of the co-authors
Responses to referee comments:

Referee #1: Cory Toth
1. The Class of Evidence found will be low in all cases, but nonetheless, this should be listed.
   A note has been added to the introduction stating that “The reviewers predicted that the class of evidence would be low, but aimed to identify and summarise this literature in one review to ensure accessibility of this clinically valuable data.”

2. No hypothesis was stated prior to the Methods – this is needed.
   The aims of the review have been stated at the end of the introduction: “The aims of this review were:
   a) to identify the evidence base in refractory neuropathic pain for three pharmacological treatments (pregabalin, lidocaine plaster and duloxetine) which are typically used at 2nd line or later in UK patients with neuropathic pain, and 
   b) to determine the efficacy, safety and tolerability of these drugs in this refractory patient population.”

3. Some explanation is needed for why the triad of pregabalin, lidocaine, and duloxetine were selected. I could understand selection of gabapentin and pregabalin, or of even TCAs and SNRIs together, but why were these three drugs targeted here?
   These drugs are typically used at 2nd line or later in UK patients with neuropathic pain as shown below:

   ![NeP - What do patients get at each line of therapy?](Image)
   NeP - What do patients get at each line of therapy?
   A line of therapy is one brand.
   This may add up to more than 100% as more than one product can be prescribed at each line

   Source: DIN-LINK September 2008

4. Upon “Hand-searching”, were the identical criteria for selection of articles used?
   The same criteria were used for references identified through hand searching. This is now stated in the Inclusion / exclusion criteria section.
5. Refractory is not well defined anywhere, but the authors should provide their definition of what “refractory” is in terms of their search. Was it simply the use of the term “refractory” in the abstract/title?

*It was not simply the use of the term “refractory” in the abstract/title. The search strategy rather aimed to locate all neuropathic pain studies, which could then be reviewed in detail to see if patients had failed on previous treatment.*

The following definition has been provided in the background and inclusion/exclusion criteria sections: To the authors’ knowledge, there are no published definitions of ‘refractory’ NeP, but there is a proposed definition of pharmacoresistant neuropathic pain “A neuropathic pain condition is resistant to pharmacotherapy when mono- or a rational combination treatment using drugs proven efficacious in RCTs fails in inducing useful pain relief from the patients/physicians point of view after an appropriate duration of treatment with adequate dosage, or if intolerable side effects occur” [8]. Owing to the lack of a consensus definition of refractory NeP, this review took a pragmatic approach to define refractory neuropathic pain more broadly as patients who had failed to receive adequate pain relief from or were intolerant to previous therapy irrespective of the duration, dose and type of previous therapy.

Further, the search strategy will be provided as additional material and the following has been added to the main body of the manuscript to confirm the method of searching: “The comprehensive search strategy, which was aimed to retrieve all studies in neuropathic pain and was not restricted by refractory terms, can be found as an additional material to this publication.”

6. Many patients or physicians believe that a patient can be refractory to a medication based upon their own loose individual criteria. Can the authors provide some discussion, and perhaps even a suggestion for the definition of “refractory” based upon their work?

A recommendation for further research both from the clinical community and from further real-world studies of this patient population towards a consensus definition of refractory neuropathic pain has been added to the discussion. A summary of the definitions in the included studies has been added to the discussion: “In addition, a proposed consensus on the definition of refractory NeP is required, since studies have been shown to present a wide variety of meanings for the term. Where definitions of refractory NeP were provided in the included studies, these focused on either lack of adequate pain relief of previous treatments (2 studies) or a combination of intolerability/lack of pain relief to previous treatments (6 studies). No studies only referred to intolerability when defining refractory NeP. Further, only one study reported information regarding the dose and duration of previous treatment, which is included in the proposed definition of pharmacoresistant NeP [30]. Such broad definitions can result in hugely diverse disease severities both within and between studies, further limiting the potential to compare between treatments. We recommend further research both from the clinical community and from further real-world studies of this patient population towards a consensus definition of refractory neuropathic pain.”

7. What was the role of the third reviewer? How were discrepancies managed?
An explanation has been added to the study procedures section. Each publication was reviewed by two reviewers, and any discrepancies in the decision for inclusion between these reviewers were resolved by a third reviewer. Similarly, all data was extracted by two reviewers and discrepancies in data extracted were resolved by a third reviewer.

8. Even though it may be obvious, an explanation of why meta-analysis was not performed should be provided.

The following explanation has been added to the review: “No meta-analysis or quantitative analysis was possible due to significant heterogeneity between included studies in terms of study design and size, and patient population (types of NeP included). Further, the inconsistencies in outcomes reported and the paucity of statistical data prevented quantitative meta-analysis. The review therefore consists of a qualitative assessment and narrative analysis to compare the studies”.

9. Why were so many articles excluded? Reasons should be provided.

Figure 1 has been updated to include the reasons for study exclusion.

10. What is EMEA license? There was no definition provided.

The EMEA (now known as EMA) license refers to the license as reported by the European Medicines Agency (EMA). An explanation has been added to table 3 and in the ‘trial characteristics’ section: The license is introduced as the “UK license, as reported by the European Medicines Agency (EMA) for pregabalin and duloxetine and the MHRA UK license for the lidocaine plaster, which was licensed by country rather than centrally by the EMA”.

11. A reference should be provided for the study reporting PGIC improvements (page 7, bottom).

This reference has been added. The sentence refers to the study by Allen titled “Pregabalin - Is it any better than Gabapentin?”

12. In the authors’ opinion, were some of the individual patients likely having non-neuropathic pain? Chronic lower back pain is certainly not necessarily neuropathic pain. Some of these issues may have further compounded the issues experienced.

Only studies in neuropathic pain conditions or lower back pain with a neuropathic component were included, but due to the small number of relevant studies available, studies including a minority of patients with non-neuropathic pain were included in the review. This has been clarified in the “inclusion/exclusion criteria” section and throughout the manuscript.

Of the two lidocaine plaster trials including patients with lower back pain, one trial enrolled patients with non-radicular LBP, who reported moderate-to-severe pain on the neuropathic pain scale at study enrolment [21], while the other enrolled only four patients of which two patients had back pain with a neuropathic component; in one patient the presence of this component was unclear and the final patient had lumbar degenerative disc disease, L4–L5 arthrodesis, and complex regional pain syndrome type 2 [22]. This information has been added to the trial characteristics section and Table 3 (overview of included studies) to clarify that very few patients included in the review had non-neuropathic back pain.
Two further studies included patients with radiculopathy and these patients are assumed to have radiculopathy with a neuropathic component as the studies state that patients with neuropathic conditions are included [28, 29]. 24% of patients (13 of 55) [28] and 1 of a total of 16 patients with radiculopathy [29] were included in these studies.

Prior to conducting the review, it was planned that only data on neuropathic pain or lower back pain with a neuropathic component would be extracted (where a minority of patients with non-neuropathic pain were also included in a study). However, in practice this was not always possible as certain studies only reported data for all patients.

13. Why are some of the pregabalin studies in Table 3 shaded, and others not? Studies which do not use the UK licensed dose of the intervention and/or do not study the use of the intervention in a licensed indication are shaded (UK license, as reported by the European Medicines Agency (EMA) for pregabalin and duloxetine and the MHRA UK license for the lidocaine plaster, which was licensed by country rather than centrally by the EMA). The footnote of table 3 has been updated with this explanation.

14. I note that a few of the abstracts they reference have subsequently been published – it may be wise to update the search for revisions. The searches for the review were run at the end of 2008 and therefore only studies available in the public domain up to this time period are included. The time taken for the submission process for this article in BMC neurology has meant that since this time further studies have been published. The review will not be updated; rather structured keyword searches in Pub Med have been conducted to identify additional studies which may be of relevance to the review and to identify if any studies included have had further work published. Studies and further publications identified have been acknowledged in the discussion. These include a discussion of results from the Toth et al full publication and the Rustagi et al study for pregabalin.
Referee #2: Maija Haanpaa

1. Delineation of the subject: Why were only three medications for neuropathic pain included in this review?
   This point was raised by a previous reviewer; please see Reviewer #1 (comment #3).

2. Delineation of the subject: On what basis was the time-frame chosen? Why not also papers published in 2009? I miss the studies of pregabalin for radicular low back pain and HIV neuropathy! In addition, it looks strange that the original papers from 1998-2008 are included but the congress abstracts from 2004-2008 were included. Give arguments for this delineation.
   Papers published in 2009 are not included since this review was conducted and completed at the end of 2008. The authors are aware of studies which have been published after this date, and those meeting the inclusion criteria of the review have been considered in the discussion. This point has been raised by a previous reviewer; please see Reviewer #1 (comment #14).

   We focused on the inclusion/exclusion criteria when assessing whether or not studies included refractory patients. We did not take this broader approach of assessing concomitant medication and pain level in spite of such medication at baseline. Therefore these studies for radicular low back pain and HIV neuropathy would not have been included even if the search was updated to include studies published after 2008.

   It is appropriate to restrict the congress abstracts searches to a more recent period as they are carried out to capture the most relevant and up to date information; it is assumed that previous congress abstracts should have been published in full at the time of the review. A Cochrane review by Scherer and Langenberg (title: Full publication of results initially presented in abstract) demonstrated that the mean time from abstract presentation to full publication ranged from nine to 36 months, therefore conference searching for this review was designed to encompass and exceed this range.

3. The definition of refractory neuropathic pain is a bit bizarre. If a RCT has included patients with allowed other medication (e.g., Dworkin 2003, pregabalin for PHN), could this study also be included, as the patients fulfill inclusion criterion of certain pain level in spite of other medications? At least if a certain percentage of the patients have concomitant medication?
   We focused on the inclusion/exclusion criteria when assessing whether or not studies included refractory patients. We did not take this broader approach of assessing concomitant medication and pain level in spite of such medication at baseline. This approach could be explored in future research.

4. It looks very strange that retrospective reports, open-label studies and reports with a few patients were included. At least number of reported cases should be higher (e.g., minimum ten cases). Usually retrospective and open-label studies are regarded as low-level source of evidence and are excluded from the systematic reviews.
The authors predicted that the evidence base for this review would be very limited. Therefore these sources of evidence are appropriately included. This explanation has been added to the inclusion / exclusion criteria.

5. Quality evaluation: Why a new classification was used instead of classic ones (e.g. Jadad score)? In addition, the classification data of each study included in the review should be provided (best in an additional table). The Jadad is a score for RCTs only, so it is inappropriate for this review including mainly non-randomised studies.

The following has been added to the critical appraisal section: The development of a new critical appraisal tool was deemed necessary after assessing current instruments. The Jadad scale [18] which is often used in quality appraisal of RCTs was unsuitable for this review as the majority of studies included in this review are not RCTs. A checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions developed by Downs and Black was found to be more appropriate [19]. However, this tool consists of a detailed questionnaire, which was inappropriate for the brief content of several of the included studies only available as conference abstracts. Hence a new scale was developed which qualitatively covers the key topics covered in the Downs questionnaire (reporting, bias and confounding effects, usefulness to the study question).

As the critical appraisal was qualitative and did not result in a single score (as in the Jadad score) or a single rating (ie low/high quality), the authors consider it inappropriate to include this level of detail in the manuscript.

6. The peer-reviewed publications should be reported separately from the ‘congress only’ publications, as peer-reviewed publications are regarded as higher-quality and higher-reliable source of data. The publications which are peer reviewed (i.e. full text journal articles) are marked in table 3. All qualitative results are then reported with trials referenced, therefore enabling the split of abstracts and peer-reviewed articles. Reporting study quality throughout the results may interrupt the flow and interpretation of the data. We report the limitations in the study designs and results throughout the discussion, and consider further weighting of results in terms of study quality to be inappropriate within this qualitative review.

7. It would be better to report how many patients support the conclusions and from what type or sources instead of reporting how many studies support the conclusions. See answer to Reviewer #2 point #6. The summary table with results (Table 6) has been updated to include the number of patients for each outcome reported.

8. Why was American Pain Society congress not included in the congress abstract search? The American Academy of Neurology was searched which was deemed sufficient to capture data presented at US conferences. Since the focus of the review is UK clinical practice, it was not thought necessary to search multiple American conferences.

9. Why were CRPS, fibromyalgia and low-back-pain patients included, although these conditions are not regarded as neuropathic pain states?
Included studies had to include patients with neuropathic pain or low back pain with a neuropathic component. A sentence has been added to “inclusion/exclusion criteria” to clarify this.

The study enrolling patients with fibromyalgia reported data for the DPN and PHN pain patients separately. Only data for DPN and PHN were extracted; this has been clarified in Table 3. There is debate concerning whether CRPS should be classified as neuropathic pain. See reviewer 1 comment 12 for more detail on this point.

10. How was the double publication confirmed?
Double publication was confirmed by matching patient populations and study design details.

11. In the reference list source information of the congress abstracts should be provided more widely; which congress and where.
The reference lists have been updated with this information added.

12. Ref. 23: the name of the paper is in capitals, should be changed to ordinary format.
This edit has been made.

13. Refs 37 and 38: this is the same publication of Rustagi. Delete the other.
This duplication has been removed.
Referee #3: Rafael Galvez

1. The authors do not state very clearly the study inclusion criteria for refractory neuropathic pain, although this is a difficult issue.
   *This point was raised by a previous reviewer; please see Reviewer #1 (comment #5 and #6).*

2. Patients were unequally distributed among the treatment groups. This is a problem because it hampers comparisons among the three groups, introducing a bias.
   *No meta-analysis was conducted in the review, so the evidence for the three treatments are not directly compared using quantitative analysis. The limitations of the included studies by study design and small sample sizes are reported and discussed. The review has highlighted the need for future, high quality trials, particularly “gold standard” RCTs and head-to-head trials in this refractory patient population.*

3. They do not report the doses of the drugs
   *Drug doses are reported in table 3.*

4. The authors might argue that, although the evidence level of their results is not high, they offer a prediction of the potential clinical applicability of the three drugs in refractory neuropathic pain.
   *The authors believe that this is implied throughout the results and discussion sections. More concrete conclusions cannot be made owing to the paucity of the data and varying study designs included.*

5. The references appears to be appropriate and mostly up-to-date. They must complete references 29, 30, 32, 45, 47, 48, 50 and 54. Reference 29 is the same as references 50 and 62
   *The reference lists have been updated accordingly.*
Editorial requests:

1. Please can you add a sentence to the competing interests section declaring that Zahava Gabriel is a current employee of Pfizer.

   *The following sentence has been added to the competing interests section: “Zahava Gabriel is a current employee of Pfizer.”*

2. Please could you add some more detail to the author contributions section. In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

   *The author contributions section has been updated in the following manner: “All three authors contributed to the conception and design of the systematic review and were involved in drafting and revising the manuscript. MP, SB and a wider review team at Heron were involved in the acquisition, analysis and interpretation of the data.”*