Author's response to reviews

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

Authors:

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

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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 second set of 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 two 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 green. Modifications from the original manuscript submission following the first set of peer-review comments remain 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 authors did state aims – this is correct. However, every scientific manuscript should have a hypothesis stated - this is needed for the reader to understand why this research was undertaken. If the research was performed to simply determine if there was an evidence base for pharmacological treatments, then this would be rather uninteresting. If there was a hypothesis that one agent would be superior, or that all agents would be equal, then at least there is a rationale for why this hard work was undertaken.

As stated in the manuscript, there were two aims of the review:
   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.

It is unfortunate that the review identified a poor evidence base in this patient population, thereby restricting conclusions to the second aim of the review. However, reviews to determine the evidence base are important as recognised by Cochrane:

The Cochrane Handbook for Systematic Reviews of Interventions states the following: “A number of factors may motivate authors to undertake a systematic review. For example, reviews can be conducted in an effort to resolve conflicting evidence, to address questions where clinical practice is uncertain, to explore variations in practice, to confirm the appropriateness of current practice or to highlight the need for future research”.  

Further, they report that there are important points to consider when planning a review, one of which is that “it is important to let people know where there is no reliable evidence, or no evidence about particular outcomes that are likely to be important to decision makers“ 1. This has been considered in our review, which highlights the lack of quality of life data for certain treatments and the need for high quality randomised controlled trials for all treatments. We have added a clearer sub-heading: “Recommendations for Future Research” within the discussion section and have adapted the conclusions and abstract to focus on this finding of the review.

Regarding the necessity to include a hypothesis, we refer to section 4.5 of the Cochrane handbook which states that there should be a precise statement of the primary objective of the review, which is present in the manuscript. It is however, “not necessary to state specific hypotheses” 1.

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2. The authors explain that one of pregabalin, lidocaine, and duloxetine is used at 2nd line or later and this was their reason for their selection. However, a review of the graph provided indicates that the two most common 2nd line agents were gabapentin and amitriptyline, agents not selected to be examined in this study. There still needs to be some justification as to why these agents were not selected to be studied.

Whilst amitriptyline is most often used first-line and gabapentin is most commonly used 1st/2nd-line, pregabalin, duloxetine and the lidocaine plaster are most commonly used 3rd-line or 4th-line or later (see figure below). In the UK, local treatment algorithms in both hospitals and primary care commonly recommend amitriptyline and/or gabapentin as first/second-line treatment options either as monotherapy or in combination. If such treatments fail to result in adequate pain relief, patients will then receive a third/fourth-line treatment option, such as pregabalin, duloxetine or the lidocaine plaster.

Source: DIN-LINK September 2008
Referee #2: Maija Haanpaa

1. If the low-level papers (i.e., case series with less than 10 patients, retrospective studies and studies reported only as congress abstracts are included, I regard this as a low-level review with little self-criticism by the authors and don’t regard it worth publishing. Some sort of excuse is that the table includes (A) referring to abstract only publications, but the retrospective/prospective setting is not clearly indicated.

Please refer to the response to referee #1, comment #1.

Limitations of the review are reported throughout the manuscript, however for clarity these have been collated into one specific section in the manuscript and added to the abstract.

We do not consider it appropriate to exclude low-level evidence where there is no higher-level evidence available. Inclusion of these studies allows readers to develop their own assessments based on the best evidence available and so supports the planning and conduct of future, higher-level studies.

2. The concept refractory neuropathic pain still remains vague, artificial and obscure in this work, which includes only few publications deserving to be included in a systematic review. To be honest, what does this paper add to the current knowledge???

The concept of refractory NeP is a challenging subject, which we addressed in a comprehensive and unbiased manner using systematic review methods. To our knowledge, no other systematic reviews have focused specifically on ‘refractory’ NeP and recent reviews of treatment efficacy in NeP, have offered little focus on the refractory patient setting. Albeit of lower quality, clinicians interested in this area would find it difficult to locate the existing, available studies as they are typically reported as conference abstracts. This review brings this evidence together in a single publication, which should bring this important topic to the attention of both researchers and clinicians.

The review both highlights and recommends the need for further research from the clinical community and from further real-world studies of this patient population towards a consensus definition of refractory neuropathic pain. Additionally, the review examines the commonly used definitions of refractory as reported in the included studies in order to guide readers as to where the definition currently stands in this disease area according to studies enrolling the patient population in question. We have added a clearer sub-heading: “Recommendations for Future Research” within the discussion section and have adapted the conclusions and abstract to focus on this finding of the review.

As discussed above in response to referee #1, The Cochrane group recognise reviews conducted to highlight the need for future research and “to let people know where there is no reliable evidence”. We therefore disagree that lower-quality publications should not be included in this systematic review where there is an absence of higher-quality evidence in this specific refractory patient population.
To our knowledge, there are no published definitions of ‘refractory’ NeP, however 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”.

Therefore, owing to the lack of a consensus definition of refractory NeP, our review took a pragmatic approach to define refractory NeP 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, due to the limited number of studies expected to be available, all studies assessing ‘refractory’ patients using alternative definitions or where undefined were also included in this review.

**Editorial requests:**

None.