PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomized clinical trials
AUTHORS	Onakpoya, Igho; Thomas, Elizabeth; Lee, Joseph; Goldacre, Ben; Heneghan, Carl

VERSION 1 – REVIEW

REVIEWER	Svjetlana Dosenovic, MD Resident, Department of Anesthesiology and Intensive Care University Hospital Center Split, Split, Croatia
REVIEW RETURNED	07-May-2018

GENERAL COMMENTS	Summary The authors invested quite a lot of effort in this rapid review to reassess the evidence for efficacy and safety of pregabalin in the management of various neuropathic pain conditions in light of recently emerging safety concerns. There are several points that need to be addressed before the article could be considered for publication. Since I was a part of the team of three reviewers during the previous submission of this manuscript, my comments this time are related to action the authors undertook according to suggestions during the previous submission. Specific points and suggestions that should be addressed in order to improve the manuscript are provided below. Major comments -Title: Please remove the word „systematic“ from the title and use the term “rapid review” to describe the study type. Although aspects of systematic review methodology are present in this study, the average reader would be misguided by this term. -Please provide a reference in the text to the unpublished protocol. Additionally, I did not see a supplementary file with a protocol among the available files so please attach it to the next submission. -Page 7, lines 51-53: The authors presented a summary risk of bias, as well as the risk of bias for each RCT in Figures 2 a and b. Please provide a Supplementary table with assessments of each RCT that includes supporting comments for judging the RoB. - Please add to your limitations that the efficacy and safety of pregabalin were not analyzed according to specific neuropathic pain

	conditions i.e. only 2 subgroups (central and peripheral neuropathic pain) were used. Minor comments -Page 18, line 12. Please correct the paragraph name since it is still named HADS, but describes another scale as well. -Page 20, rows 50-55. The authors state that „Finnerup et al 49 concluded that there was modest evidence supporting the use of pregabalin for treatment of neuropathic pain; however, the authors used GRADE criteria to assess the strength of recommendation but not the quality of the evidence“ although the study methods report: „We used GRADE to rate the quality of evidence and the strength of recommendations.“ Please check and correct this. -Page 22, lines 5-7: „This rapid review has limitations due to its streamlined methods and search strategy. Firstly, the lack of a published a priori protocol...“ The fact that you did not publish the protocol a priori is not due to limitations of a fast rapid review methodology. There are many rapid reviews with a published protocol so please correct this. -Page 22, lines 18-20: “we undertook the same rigorous approach using Cochrane criteria for other systematic reviews within the time constraints“. Please rephrase this statement as it is not completely accurate and gives the readers the wrong impression. No matter how time-constrained the approach, the publication of a protocol is a very short and important step that has been skipped.

REVIEWER	Steven P. Cohen Johns Hopkins, USA
REVIEW RETURNED	09-Jun-2018

GENERAL COMMENTS	The authors have performed a comprehensive systematic review and meta-analysis on the use of pregabalin for neuropathic pain. As the authors acknowledge, there have been many reviews, including systematic reviews, on the use of pregabalin, which have concluded the same thing this shows- it is effective. The article is well-written and well-referenced, and adverse events and secondary outcomes are included. There are 2 issues I think the authors should consider. In the discussion, the authors note the findings of similar reviews, and state the differences between those and this one. However, since there are so many, it is not really clear why another SR and MA on this question is needed. Several SRs have been published on specific conditions. Pregabalin does not appear to be effective for radicular pain, but some of those studies did not separate out leg and back pain. This is important, as radicular pain is generally a mixed pain condition (axial, non-neuropathic back pain from degenerative discs and facet joints and neuropathic pain from nerve root irritation). The bigger picture is that it would have been helpful to do subgroup analyses to figure out who responds and who doesn't. Since there is so much data, this can be done by gender, age, diagnosis, dosing, and other variables. The authors use the IASP definition for neuropathic pain, but the IASP also states that "sciatica" is not a good term (non-specific).

	Radicular pain is the correct term. A minor issue is that for this to be more helpful for clinicians, the authors should try (as Finnerup et al. did) to show how many would benefit from therapy. This can be done in several ways, including NNT and NNH. Overall, I think this is a very well-done study.

REVIEWER	Harsha Shanthanna McMaster University Canada
REVIEW RETURNED	03-Jul-2018

GENERAL COMMENTS	1. INTRODUCTION It is accepted that pregabalin is recommended as a first line option for management of neuropathic pain, which you also note in line 33 of page 4. A systematic review published in 2015 included latest literature and also synthesized evidence and gave out recommendations using the GRADE approach. Finnerup NB, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015 Feb;14(2):162-73. NICE has published recommendations based on existing evidence and it was last updated in April 2018. https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations#ftn.footnote_3 Giventhis evidence, can you substantiate the need for your review and what does it add to the existing literature about pregabalin for neuropathic pain, apart using GRADE approach to report the quality of evidence for each outcome? "Rapid reviews may be driven by clinical urgency and intense demands for uptake of technology or may be determined by limited time and resources to conduct full systematic reviews" [*Implementation Science*2010**5**:56]. As pregabalin is already included as the first line treatment in most guidelines, it is not clear why a rapid review was necessary in this scenario? 2. METHODS The specific methods employed to make this a rapid review, apart from not searching the grey literature, is unclear. In the abstract you say: study comparators can be: Pregabalin or placebo, with or without co-interventions. However, in the selection of studies (line 24-26, page 5) you mention only efficacy studies (placebo controlled only)- We included phase III double-blinded placebo-controlled RCTs (efficacy studies). **Population:** You mention that you included - studies on neuropathic pain based on the definition of the International Association for the Study of Pain (IASP) definition and mention the list of clinical diagnoses which have been listed as possible

causes of neuropathic pain. As per the redefined IASP definition, the neuropathic pain is a spectrum from definite, probable, and possible neuropathic pain. For example, most post-surgical pain comes under mixedetiology or only within possible neuropathic pain [Serra, T O. "Neuropathic pain: redefinition and a grading system for clinical and research purposes." Neurology 70.18 (2008): 1630-5]. This in itself leads to significant heterogeneity. There are multiple reviews suggesting that pregabalin or gabapentin does not help chronic post-surgical pain, in contrast to its finding for post herpetic neuralgia or diabetic neuropathy.
I would suggest excluding studies on possible or probable neuropathic pain by provide a rationale how it was considered similar with classical neuropathic pain conditions.
Line 33-34 page 5: We included RCTs irrespective of study size and duration. I am not sure what it is supposed to mean? Duration of chronic pain? Treatment? or follow up?
Line 35-37 page 5: If the reason for excluding phase 4 studies was for non-blinding, is it not better to state that we excluded any non-blinded studies? What if there is a possibility that a large and well done (blinded) phase 4 study has been eliminated?

Outcomes:
Primary: Apart from pain, specify what adverse effects were specifically considered for outcomes?
Functional improvement has not been considered, although it is widely appreciated that it is important; how do you justify?
Study Selection and Data Extraction: Two selected studies and three extracted data; but was it done in duplicate? You also mention that two reviewers (IJO and ETT) independently entered the data onto RevMan software and independently cross-checked each others entry. If three extracted data, was it done simultaneously by three investigators?

Data Extraction: We extracted data on extracted data on study ID, settings, populations, interventions, outcomes and results- what do you mean by study ID?

Pooling: Why was SMD considered over Mean differences for pain? MD can be obtained by converting all pain scales into a commonly used scale. SMD is difficult to interpret as it is in units of standard deviation rather than any actual units [Egger M, Smith GD, Altman D: Systematic Reviews in Health Care: Meta-Analysis in Context. 2008, Wiley. Com]. Also see below for interpreting results for pain relief.
Change scores versus end scores: You state that used to change scores and whenever SDs were not available you imputed using other studies. There are also limitations to this assumption. Could you tell us SD's of how many studies were

	imputed vs. reported in studies? 3. RESULTS: Line 11-12, page 8: 21 studies were included in the quantitative analysis (also shown in figure 3), but the flow chart (figure 1) says 26 studies? **Pain relief**: In lines 13-16, page 8, you state that-'' Meta-analysis showed a significant reduction in pain scores with pregabalin compared with placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001, I2=88%: Figure 3)". It must be kept in mind that it is not pain scores, but only SD units for pain relief. Also, if you interpret the value of SMD based on Cohen's d rules of thumb, an SMD of 0.2 represents a "small" effect, an SMD of 0.5 represents a "medium" effect, and an SMD of 0.8 represents a "large" effect [*BMC Medical Research Methodology*2014**14**:30]. In view of this, your results suggest only a small to medium effect that is statistically significant. Please change this interpretation appropriately for both the abstract and the main text. Similarly, in the GRADE chart for pain (page 13), you mention the outcome as 'mean pain score', but which score would you be referring to? VAS? NRS? 0-10? Or 0-100? In contrast, you have done it appropriately for sleep interference (page 17). **Adverse events** (figure 4) pooling: Each adverse event is different from another. I think it may not be appropriate to combine all adverse events into a single pooling analysis. There is large heterogeneity for both measurements and clinical risk. I also observe that there is no mention of indirectness in your GRADE chart due to variations and validity with which each adverse outcome is measured. I do agree with combining all the adverse effects leading to withdrawal, as the outcome is withdrawal-which has clear validity of measurement. **Reporting p values**: It is appropriate to use only 3 decimals. 4. DISCUSSION: Line 7-8 page 20-"The evidence from published RCTs suggests that pregabalin reduces pain scores in patients with neuropathic pain". Evidence suggests pregabalin improves pain or decreases pain (not pain scores). Line 10-" The effect is significant in peripheral neuropathic pain",-revise to say there was a statistically significant effect. Line 11-take out (P=0.08). How did the authors chose to decide on publication bias is not clear. Further, the funnel plot is asymmetric but there does not seem to be any reference to that in the results section. 5. LANGUAGE At several parts, the sentence does not read completely and would need some language edits or revision, such as:

	"In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 versus (spend increased from approximately $2 billion to $4.4 billion over the same period". "We conducted electronic searches in the Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL)"-should read electronic databases. "The risk of bias for each included study was rated using Cochrane criteria"-there should be 'the' before Cochrane.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments	Authors' responses	Action
Reviewer #1		
Summary In this rapid review, the authors reassessed the evidence for efficacy and safety of pregabalin in the management of various neuropathic pain conditions in light of recent increases in reported serious adverse events and safety concerns. The evidence from randomized, placebo-controlled trials was assessed for Risk of bias and graded using the GRADE approach. The authors report very low quality evidence that pregabalin reduces pain in peripheral, but not in central neuropathic pain; low quality evidence that increases the risk of adverse events (e.g., weight gain, somnolence, dizziness…) and discontinuation because of adverse events, but the risk of serious adverse events was not statistically significant (moderate quality evidence). The authors addressed an important topic and presented up-to-date, comprehensive evidence from 28 RCTs with 6087 included participants. Currently, there are some issues that should be addressed in order to improve the manuscript. Specific points and suggestions are provided below.		
Major comments -Page 5, Introduction: The introduction is mainly focused on the increasing use of pregabalin and potential harms of the drug. Although the authors mention 5 references that support the efficacy in PDN and PHN, there are several evidence-based guidelines which recommend pregabalin as first line treatment for neuropathic pain, as well as other relevant systematic reviews and overview of systematic reviews that address its efficacy and safety; which were not mentioned at all. The authors need to reflect on the relevant evidence while writing a	We have included two subsections in the discussion: 1 -Comparison with the existing literature and; 2-comparison with existing guidelines. We have enumerated the ways in which our review is similar and differ from these	**Added the following:** **"Comparison with the existing literature** We have identified several published

background for their study, explain in more detail how their study is different and justify why it is needed. Currently it is not clearly demonstrated why this study is needed. Examples of relevant studies with links: • Guidelines: “EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision” (https://www.ncbi.nlm.nih.gov/pubmed/20402746), “Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society.” (https://www.ncbi.nlm.nih.gov/pubmed/25479151), “Neuropathic pain-pharmacological management: National Institute for Health and Care Excellence, 2013. Updated February 2017” (https://www.nice.org.uk/guidance/cg173/evidence/full-guideline-pdf-191621341), “Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.” (https://www.ncbi.nlm.nih.gov/pubmed/21482920). • Systematic review by Finnerup et al. from 2015 (“Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis”, http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(14)70251-0/fulltext) provided evidence for “a strong recommendation for use and proposal as first-line treatment in neuropathic pain for pregabalin based on the GRADE classification”. Their recommendations are based on the following findings: “18 of 25 placebo-controlled randomised trials of pregabalin (150–600 mg/day) were positive, with high final quality of evidence. There was a dose response gradient (higher response with 600 mg daily than with 300 mg daily; data not shown)… Combined NNT was 7·7 (95% CI 6·5–9·4) and NNH was 13·9 (11·6–17·4)…Tolerability and safety was moderate to high.” • A 2013 Cochrane overview of Cochrane systematic reviews of antiepileptic drugs for neuropathic pain and fibromyalgia found “reasonably good second tier evidence for efficacy (of pregabalin) in painful diabetic neuropathy and postherpetic neuralgia. In addition, for pregabalin, we found evidence of efficacy in central neuropathic pain and fibromyalgia.” (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010567.pub2/full)		reviews assessing the effectiveness of pregabalin the management of neuropathic pain, and our results are partly consistent with these. Zhang et al and Wang et al showed that pregabalin was more efficacious than placebo for treatment of DPN-associated pain and PHN-associated pain respectively; however, the two reviews did not base their results on changes from baseline between groups. Semel et al and Freeman et al also concluded that pregabalin was more effective than placebo for neuropathic pain;

• Safety: Zaccara et al. conducted a systematic review of RCTs in which they investigated the adverse event profile of pregabalin (http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2010.02966.x/full). The authors reported that "Of 39 AEs, 20 (51%) were significantly associated with pregabalin (dizziness, vertigo, incoordination…)…There was no significant association between serious AEs and pregabalin. There was a selective dose–response pattern in the onset of pregabalin AEs, with certain AEs appearing at lower doses than others." • Another safety study pooled results from 31 phase II, III, and IV RCTs of pregabalin in peripheral NeP sponsored by Pfizer conducted by May 2012 ("A Comprehensive Drug Safety Evaluation of Pregabalin in Peripheral Neuropathic Pain" (http://onlinelibrary.wiley.com/doi/10.1111/papr.12146/full). Their results identified "identified 9 AEs with a risk difference, for which the lower limit of the 95% confidence interval (CI) was > 1%: dizziness (risk difference [95% CI]: (17.0 [15.4 to 18.6]), somnolence (10.8 [9.5 to 12.1]), peripheral edema (5.4 [4.3 to 6.4]), weight increase (4.7 [3.9 to 5.5]), dry mouth (2.9 [2.1 to 3.8]), constipation (2.3 [1.5 to 3.2]), blurred vision (2.2 [1.6 to 2.9]), balance disorder (2.0 [1.5 to 2.5]), and euphoric mood (1.6 [1.2 to 2.0]).		however, both reviews did not account for the quality of the included primary studies. Finnerup et al concluded that there was modest evidence supporting the use of pregabalin for treatment of neuropathic pain; however, the authors used GRADE criteria to assess the strength of recommendation but not the quality of the evidence. In an overview of Cochrane reviews, Wiffen et al concluded that there was clinical trial evidence supporting the use of pregabalin for treatment of some aspects of neuropathic pan; however, the authors did not rate the quality of the evidence for

		the outcomes reported. Two reviews that examined the safety profile of pregabalin concluded that pregabalin use was significantly more associated with adverse events than placebo; however, both reviews did not rate the quality of the evidence for the outcomes reported **Comparison with existing guidelines** We identified several guidelines that recommend the use of pregabalin for treatment of neuropathic pain, and some of their specification s are consistent

		with our results. For instance, the European Federation of Neurological Societies (EFNS) guideline based on data from comparative studies recommended pregabalin as first line treatment for neuropathic pain; however, the guidance assessed only the level of, and not, the quality of the evidence, and also notes that there are too few large scale comparative studies to make definite conclusions about the benefits and harms. Similarly, the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine,

		and the American Academy of Physical Medicine and Rehabilitatio nn guidance recommends pregabalin as first line treatment based on levels (and not quality) of the evidence; however, they guidance recommends that clinical trials of longer duration should be conducted. The Canadian Pain Society (CPS) guidance recommends pregabalin as first-line treatment for neuropathic pain, but acknowledge s that paucity of longer-duration trials limit the conclusions that can be drawn about its benefits and harms on the long-term.”

- Page 5, Introduction: It is not clear why a rapid review with meta-analysis was chosen instead of a systematic review. The main advantage of a rapid review would be a quick insight into new facts in expense of potential limitations associated with rapid reviews. However, there are not many new RCTs (such as Mathieson 2017) included in this rapid review compared to the older studies. Conducting a priori defined, high-quality systematic review with the aim of updating and critically reviewing the existing evidence base would give a greater impact to your study, as well as including RCTs with active comparators and a dose-response analysis.	We undertook the rapid review because the research is part of an investigation being conducted by the BMJ about the effectiveness and safety of pregabalin, and a quick reappraisal of the evidence for benefits and harms is required, especially in the UK where doctors are calling for access to the drug to be restricted. We have already noted lack of dose-response analysis in our limitations section.	Moved section of introduction into discussion
- Page 2, Abstract: According to 'PRISMA for Abstracts' checklist, some important information is missing from the abstract. Specifically, eligible outcome measures are missing; summary of main outcomes should be presented in terms meaningful to patients and clinicians (direction and size of the effect), as well as funding and registration details. Please see the following link: http://www.prisma-statement.org/Extensions/Abstracts.aspx.	We have added the main outcome measures to the abstract; we believe our reporting of the main results are clear enough to understand because we reported the direction of effects for each outcome reported – we have shortened the abstract to 298 words (BMJ Open format) We have uploaded the unpublished protocol as a supplementary file.	Added the following to the abstract: "Our primary outcomes were pain and adverse events. Secondary outcomes included sleep disturbance, quality of life, anxiety and depression, and discontinuations because of adverse events." We have formatted the abstract in line with BMJ Open guidelines.
- Page 2, Abstract: Please include in the results presented in the abstract neuropathic pain conditions studied in included RCTs.	Included	Added the following:

		"The neuropathic pain conditions studied were diabetic peripheral neuropathy, post-herpetic neuralgia, herpes zoster, central neuropathic pain including sciatica, post-stroke pain and spinal cord injury-related pain."
-Page 4, What is already known on this topic: Please add a sentence that evidence-based guidelines recommend pregabalin as first line treatment for some neuropathic pain conditions.	Added. Note that this section changes in BMJ Open to "Strengths and limitations"	Evidence-based guidelines recommend pregabalin as first line treatment for some neuropathic pain conditions.
-Page 5, line 7, Introduction: please write the acronym at first time mention (e.g. FDA).	Revised	United States Food and Drug Administration
-Page 6, Methods: I cannot seem to find any reference to a study protocol. Please justify why there is no registered protocol for the rapid review? You adhered to many methodologic steps characteristic for systematic reviews, yet there is no a priori protocol available. It is possible to register a protocol in PROSPERO database. Please add this to your limitations section as missing a priori protocol is a possible way of introducing selective outcome reporting in systematic reviews, as well as rapid reviews.	We have uploaded the unpublished protocol as a supplementary file. We have revised the limitation to reflect the fact that the protocol was unpublished.	Added the following to the limitations section: "Firstly, the lack of a published apriori protocol could have

		introduced selective outcome reporting bias in this rapid review; nevertheless, most of the outcomes reported in this review have been listed as outcomes of interest to be considered when designing trials of neuropathic pain interventions ”
-Page 6, line 14, Methods: Please write a full name of the database searched in the Cochrane library. I assume it was the Cochrane Central Register of Controlled Trials (CENTRAL), as indicated in the abstract. -Page 6, line 24, Methods: Please explain why only placebo-controlled trials were eligible; but not randomized trials investigating head to head comparison against other interventions.	We have added the full name of Cochrane. We examined efficacy, not effectiveness. We have added efficacy in brackets	
-Page 6, line 40, Methods: Please explain the rationale for excluding studies that combined pregabalin with other types of interventions.	Because the effects of such combinations (positive or negative) would not be exclusively due to pregabalin	Revised: “We also excluded studies that combined pregabalin with other types of pain intervention because the effects of such interventions would not be exclusively due to the actions of

		pregabalin...”
-Page 6, line 46, Methods: Please provide a reference and explanation for choosing “validated scales” for pain outcome.	Revised	“Our main outcomes were pain (as measured using validated scales because such scales enhance the credibility of the measured outcomes)”
-Page 6, lines 46-53, Methods: Also explain the reasons for not including other relevant outcomes for neuropathic pain (such as physical functioning/disability, according to NeuPSIG (https://www.ncbi.nlm.nih.gov/pubmed/20851519) and IMMPACT recommendation (https://www.ncbi.nlm.nih.gov/pubmed/14659516), which are important for standardizing the reporting of outcomes in conducted trials in neuropathic pain and chronic pain, respectively).	Because this was a rapid review, we limited the number of outcomes to include. Fortunately, most of our outcomes are outcomes of interest for trials of neuropathic pain (https://www.ncbi.nlm.nih.gov/pubmed/27659719). As the reviewer suggested, we have included a statement in the limitation about the possibility of selective outcome reporting because of the rapidity of the review process.	
-Page 7, line 31, Methods: You mention sensitivity analyses, but I did not find such findings described in the results. Please explain this.	Thank you. We have included the reports of sensitivity analyses, and added an appendix table 2: Appendix Table 2in the original submission now becomes Appendix Table 3 in the revised manuscript.	
- Page 7, Methods: Please define statistical significance threshold.	Defined	“We used a value of P=0.05 as our threshold for statistical significance.”
-Page 8, line 33, Results: Please correct to spinal cord injury pain or spinal cord injury-related pain.	Corrected	
-Page 10, line 50, Results. Why is “VAS anxiety scale” categorised as a Quality of Life measure? Consider reporting this tool for measuring anxiety together with the results for HADS scale in a paragraph named Emotional functioning or Psychological assessment (ref:	We have moved this to the anxiety and depression section of the results.	

https://www.ncbi.nlm.nih.gov/pubmed/20851519 , https://www.ncbi.nlm.nih.gov/pubmed/14659516).		
-Page 12, lines 22-24, Discussion: Please add dry mouth to the list of significant adverse events.	Added	
-Page 28, Table 1. Some outcome measures were not completely extracted from RCTs, for example Mathieson 2017: workplace absenteeism and use of other treatments are missing. Please check and correct this.	We did not report all outcome measures – unpublished protocol attached as supplementary file.	None
Reviewer #2		
Comments: The authors have performed a systematic review and meta-analysis on the use of pregabalin for neuropathic pain. Given the increase in use, this is an important area. Several systematic reviews have been published on particular conditions (some are noted, some are not), but one important one is missing- the Finnerup et al. Lancet Neurol 2015 paper from the IASP group. This contained SR's on many different treatments, and included 25 articles for pregabalin. They included some trials not included in this review (Vranken, Freynhagen) as well as several studies that were registered but not published (they obtained the data from the sources because it was thought that this would minimize publication bias). Based on the years published, it would appear that this review includes only 2 studies that they did not include.	We agree with the reviewer. However, no review has rated the quality of the evidence for each outcome like we have done in this review. In addition, we have added two new sections that compare our review with existing reviews and guidelines.	As above
There are a few questions I have regarding the studies included. The Finnerup IASP review did not include studies evaluating acute herpes zoster. Although this many involve a neuropathic component, the pain is also nociceptive (lesions causing tissue damage), and the short time frame (the Kanodia study included patients with pain < 72 hours) required for inclusion in some studies is not good to evaluate a treatment (because the placebo group is also statistically likely to get better). A second question is that some other studies (e.g. Malik K et al. Anesth Pain Med, which unlike every other study in this review was not industry-sponsored) were excluded, and the Rauck study (ref 33) evaluated gabapentin, not pregabalin.	We thank the reviewer for highlighting this. We have included a section that compares our findings with those of existing reviews (including Finnerup). The Kanodia study was not included in the meta-analysis for pain because of inadequate data; its results were reported narratively, and in Appendix Table 3 Malik et al was a phase IV study, and therefore does not meet our inclusion	See above. Added the following: “Of note, the results of the only published charity-funded phase IV placebo-controlled trial that assessed the effectiveness of pregabalin in management

	criteria (Phase III). However, the results of this charity-funded study are at variance with those of industry-funded counterparts. This is why access to CSRs of published trials should be granted – we have highlighted this in the "implications for research" section. Rauck study evaluated gabapentin, but there was a pregabalin arm. We compared the pregabalin arm with placebo for this review.	of neuropathic (radicular) contrast our meta-analysis results – there was no significant difference in pain scores between groups."
Other comments 1. Please note whether this review was registered.	The review was not registered. We have included this in our limitations; and have uploaded the initial protocol as a supplementary file.	As above
2. Page 5, lines 20-22: This is not a sentence.	Deleted	
3. Page 6: Was there any particular time frame that constituted the primary outcome? I think it's important to specify this, and there is a big difference if it's shown to alleviate pain for < 4 weeks compared to 12 weeks (which is typically how long studies last).	We have included sensitivity analyses based on study duration (12 weeks or more; because this was the mean duration of intervention), and added a table as an appendix (Appendix Table 2). Longer studies should last up to 12 months because the drug is prescribed for that long in the UK for example	See results and Appendix Table 2
4. On the same page, it states that pain was measured on validated scales, and though the authors report the results of studies using the different measures separately on page 9, since they were combined (figure 3), they should note how they were converted or standardized for meta-analysis.	We combined data based on NRS pain scores as stated in our results. Some authors used 0-10, while others used 1-10. Nevertheless, we used pre- to post-intervention changes for meta-analysis. We have noted this in the methods.	Added the following to the methods: "We used pre- to post-intervention changes to assess intervention effects between pregabalin and placebo."
5. All neuropathic pain is not the same (e.g. radiculopathy is more challenging to treat than diabetic neuropathy). Any consideration for doing some subgroup analyses to determine if certain conditions (e.g. radiculopathy and certainly herpes zoster are	We set out to compare the overall effects of pregabalin on central and neuropathic pain. We did not set out to compare outcomes by medical condition, but intend to do this in the	None

almost never purely neuropathic, and the latter might be more nociceptive) or populations (e.g. age or gender) are more likely to benefit?	future.	
6. Any possibility, similar to the Finnerup review, of reporting the numbers needed to treat and harm?	We did not set out to compute NNTs and NNH. We have now included NNHs in our summary of findings tables for dichotomous outcomes. Because we measured pain using continuous outcomes, we are unable to compute NNTs.	
7. Bottom of page 10: If there is a separate section on HADS (Hospital Anxiety Depression Scale), why is QoL measured using a VAS anxiety scale listed with QoL and not anxiety? Separately, the last letter of HADS stands for "scale", not "scores".	We have moved VAS anxiety to the anxiety and depression section.	
8. Page 10: The authors note more deaths in the pregabalin group, which not surprisingly did not reach statistical significance (studies are very poor for detecting rare events). Please note (if provided) whether the authors of the study felt these deaths were related, unrelated, or possibly related to the study drug.	This is a further classification of adverse events in clinical trials. While we acknowledge this suggestion, we have not investigated whether they were related to the study drug: this is another issue that requires more extensive investigation, and is outside the scope of our initial intent.	None
9. In the 1st page of the discussion, the authors note that for central pain, the p-value is 0.08 (NS). This obviously can be a function of the smaller number of patients, but in reading through the paper I do not think the patient numbers are broken down by peripheral vs. central neuropathic pain	All subgroup analyses by pathway are reported in Appendix Table 1. We chose not to report all the comparisons in the text because of word count limits	None.
10. Pages 12-13: As noted above, studies were missed (not may have been) but not searching registries (in addition to the other aforementioned studies).	This is common with all systematic reviews. You are never 100% certain of capturing all available studies.	None.
11. Perhaps evaluating the type of neuropathic pain pregabalin relieves (e.g. stimulus-dependent pain such as hyperalgesia or allodynia), or spontaneous pain would be an area of future research?	We have included this in the implications section.	Added the following: “Studies investigating the type of neuropathic pain pregabalin relieves (e.g. stimulus-dependent pain such as hyperalgesia or allodynia), or

		spontaneous pain could be an area of consideratio n for future research.”
12. In terms of implications for clinical practice, the Gilron studies that compared gabapentin and morphine to the combination, and gabapentin and nortriptyline to the combination, found higher rates of adverse effects in the combination groups.	We did not include comparative studies in the review. We assessed pregabalin efficacy.	
Reviewer #3		
Comments: This is a potentially informative meta-analysis of pregabalin for neuropathic pain, emphasising the significant increase in adverse effects which may outweigh the modest analgesic benefits.	Thank you.	
The authors state correctly that there are concerns about increased risk of harms when pregabalin is used with opioids (prescribed or illicit use) however the search strategy did not include trials that combined these within intervention arm to gain insights into absolute risk of harms.	Thank you.	
The authors did not cite the most authoritative recent review of drugs for neuropathic pain by Finnerup et al (Lancet Neurol. 2015 Feb;14(2):162-73) which included 25 RCTs of pregabalin. In the Finnerup review, evidence was graded as high quality, with outcomes reported as NNT / NNH: for pregabalin these were NNT 7·7 (6·5–9·4) and NNH 13·9 (11·6–17·4). The Finnerup review didn't provide as much detail on adverse events as this current manuscript (which is helpful) but estimates of efficacy were broadly the same and so it's not clear what new sights are provided overall.	Thank you. We have now cited Finnerup and other published reviews and guidelines, and compared our findings with those. The Finnerup studies used GRADE criteria to provide recommendation. Our review rates the quality of the evidence for each outcome assessed.	As above

VERSION 2 – REVIEW

REVIEWER	Svjetlana Dosenovic, MD Department of Anesthesiology and Intensive Care, University Hospital Split, Split, Croatia
REVIEW RETURNED	10-Sep-2018

GENERAL COMMENTS	All of my previous comments have been dealt with adequately. I have two additional minor comments. 1. There are several typos and minor grammar errors in the manuscript (e.g., page 4, line 35: attributed to?; page 5, line 33,

	definition is repeated twice within the sentence). 2. The protocol is mostly written in the future tense, but there seems to be a point where past tense is used:" Any disagreements were resolved through discussion." Please check and correct accordingly.

REVIEWER	Steven P Cohen Johns Hopkins, USA
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	The authors have sufficiently addressed my few concerns.