

Dear Prof. Loder,

**Re: Manuscript ID BMJ.2017.039974: Corticosteroids for treatment of sore throat: a systematic review and meta-analysis of randomised trials**

Thank you for the invaluable comments that have enabled us to improve our manuscript. We are grateful for the opportunity to resubmit. Below are the detailed responses to the editorial team and reviewers comments; the comments are in bold and our responses follow. In addition, we highlighted all changes in the text of the manuscript using track changes in MS Word.

Yours sincerely,

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### ***Authors' Reply to the editorial team Comments***

- **Several editors thought the research question was relevant, especially since there is new concern about the safety of NSAIDs and a desire to avoid the use of antibiotics when appropriate.**

Thank you, we agree. We have added the following to emphasize that NSAIDs/acetaminophen are not benign:

*“These medications provide limited pain relief but also sometimes cause serious harm.<sup>1 2”</sup>*

- **On the other hand, there was a great deal of concern about medicalisation of sore throat. Several editors suggested that self-management of mild sore throat is the goal of most primary care clinicians. You might emphasise that the majority of these studies come from an ED setting, where presumably most patients had sore throats severe enough to cause them to seek such treatment.**

We agree and have deliberated extensively about over-medicalising a condition that is self-limited and often no more than an irritation. We have added the following to the concluding paragraph:

*“However patients with less severe sore throat will glean less absolute benefit from corticosteroids. Thus the balance of risks and benefits almost certainly depends on the severity of the patient’s sore throat.”*

- **There also was worry about potential side effects of corticosteroids. We would like you to provide more information about exactly how side effects were queried or sought in each of the included studies. Please also comment on the possibility that longer term side effects or side effects related to frequent episodic use of steroids might have been missed in these studies.**

Thank you for the helpful comments. We have expanded on the issue of certainty around adverse effects in several places:

We added below text to the methods:

*“We included any adverse events that were reported by the authors.”*

In the results:

*“No study included patient-reported adverse events.”*

In the discussion:

*“There was no increase in the few serious adverse effects in the included RCTs, patient-reported minor adverse effects might not have been captured. Further, potential adverse effects that have a longer lead time, are more likely to occur after repeated use, or are serious but very rare and would not have been captured in the RCTs.”*

We have also made it clear in the concluding paragraph that we are referring to serious adverse effects:

“...the available evidence suggesting that serious adverse effects are very rare, ...”

- **Please also make clearer, perhaps in the abstract, what dose and drug and route was most commonly used in the studies. Several people mentioned that they read the entire review without having any idea what was meant by a single dose of steroids. Which steroid? Which dose? Parenteral or oral? It is not until one gets to the table that this is clear.**

We have added below text to the result section on page 7 to clarify the corticosteroid type, dose, and route of administration:

“Oral dexamethasone (single dose of 10mg for adults and 0.6mg/kg, max. 10 mg for children) was the most common intervention (5 studies) followed by single dose intramuscular injection (IM) of dexamethasone (3 studies).”

We have also added a short description of the most commonly used drug and route to the abstract:

“...patients receiving single low dose corticosteroids (oral dexamethasone with a maximal dose of 10mg being the most common interventions) ...”

- **There was worry that busy doctors might forget that it was a single dose in most of these studies and end up prescribing a medol dosepak, or refilling steroids over the telephone for patients whose symptoms continue. We thought this should be addressed and discouraged in the accompanying education piece.**

This has been addressed in the revision of the joint guideline manuscript linked to this systematic review within the Rapid Recommendation publication package: both under the “What You Need To Know?” box and the section “Understanding the recommendation”.

- **We would also like more detail on the therapy in the control conditions. What is treatment as usual? Which patients got other pain therapy?**

We have added below text to the results section on page 7 to clarify the usual care reported in trials. Also, percentage of patient receiving antibiotics and analgesics in control arm is provided in Table 1.

“All patients in three RCTs received both antibiotics and analgesics as the usual care,<sup>3-5</sup> all patients in two RCT received only antibiotics as the usual care and analgesics were prescribed at physician’s discretion.<sup>6,7</sup> In the remaining five trials prescription of antibiotics or analgesics as a part of usual care group were at physician discretion.<sup>8-12</sup>”

- **Several editors felt this didn't add much to the 2014 Cochrane review. Can you elaborate on why this does add?**

Our review adds several important aspects over the previous Cochrane review, published in 2012 (<https://www.ncbi.nlm.nih.gov/pubmed/23076943>). First, we include two additional RCTs – one that should have been included but was not in the previous review and one that extends the applicability of the findings to a broader population. Although there are only two additional RCTs, our meta-

analysis includes approximately twice as many participants (1426 vs. 743). Second, the Cochrane review is now five years out of date. Third, the evidence for benefit from our review, but not in the previous, extends to patients who present to GP visits. The vast majority of patients with sore throat present to a GP rather than the ED – in fact sore throat accounts for up to 5% of GP visits – so the applicability of the evidence to this patient group is an important question. The evidence now suggests that the relative effects are similar between ED patients and outpatients. Fourth, we analysed several important subgroups that experts have postulated might be important, including: age (children vs. adults), administration route (oral vs. parenteral), presence or absence of culture-positive for a bacterial pathogen or direct antigen test for GAS, initial setting (emergency departments vs. family practice), and place of subsequent care (hospitalized vs. outpatient). The Cochrane review only evaluated route of administration as subgroup for all outcomes.

- **We were very concerned about the reviewer who pointed out the 2003 paper that should not have been picked up if the bridging search in fact began in 2010. Can you reassure us about this matter?**

As mentioned in the methods section, we reviewed reference lists from relevant reviews for additional eligible trials. In our searches, we found two systematic review of randomized trials<sup>13 14</sup> that included Ahn 2003 trial. The article was in Korean language and we asked a Korean language colleague to make sure this is a randomized trial. The Korean article full-text is available here: <http://www.kjorl.org/journal/view.php?number=2530>.

The relevant section in the methods when translated, reads: "Each patient was randomly divided into three groups: A, B, and C, and 375 mg amoxicillin / clavulanic acid and 650 mg acetaminophen were administered to all patients three times daily for 2 days. group A, dexamethasone was administered orally 5 mg / day for 2 days, group B received dexamethasone and 200 mg ibuprofen for 2 days, group C received ibuprofen for 2 days."

The English version of the abstract that says the groups were arbitrarily divided is poorly translated from Korean to English, which is presumably the reason why it was previously excluded.

- **We felt that the conclusion was overly positive given the lack of evidence about harms and that it would be more appropriate to say that the balance of benefits / harms is not well enough established.**

We agree – and this is actually reflected in the weak recommendation of the Rapid Recommendation (guideline manuscript) linked to this systematic review. In addition to the additional comments above added throughout the text that highlight the lack of direct evidence about harms, we have added the following to the conclusion:

“More high quality data would be helpful to fully understand the balance of benefits and harms according to patient severity, especially in primary care settings.”

- **We wondered about generalisability since the review excluded patients most likely to have very severe sore throat, e.g. those with mononucleosis, post-intubation, etc.**

While many of the patients in the study probably did have severe sore throat because they presented to the ED, 655 (46%) of the total population was recruited from primary care settings. Further, we tested for and did not find any subgroup effects for what might be considered surrogates of severity: presence or absence of culture-positive for a bacterial pathogen or direct antigen test for GAS, initial setting (emergency departments vs. family practice).

Please note that our review explicitly excluded patients with mononucleosis and post-intubation. In the methods, we say:

“We excluded studies of participants who were hospitalized or immunocompromised, and those with infectious mononucleosis, sore throat following any surgery or intubation (post-operative sore throat), gastroesophageal reflux disease, croup, or peritonsillar abscess.”

According to the BMJ Rapid Recommendation methodology, the PICO question was defined with the panel of the guideline, and the recommendations does not apply to these excluded populations.

- **Our statistician commented "Negative CIs the wrong way around -1.9 to -7.8, make them positive."**

Thanks for pointing the mistake. The negative signs are removed from the numbers in the abstract and results texts.

- **We would like more information on why you excluded studies of children under 5 years?**

We excluded children under 5 because they would not provide reliable outcome measurements, particularly for self-reported pain (see von Baeyer et al<sup>15</sup>). Note that we did not find any such studies regardless. In the methods, we now say:

“We excluded studies with children under 5 years old because they would not be able to provide reliable outcome measurements (especially for self-reported pain).”

- **Highly significant IM vs oral corticosteroid interaction, but between rather than within studies.**

Thank you for reiterating this issue. We mentioned this in the discussion, the last paragraph on page 10 (*We explored, and were able to dismiss, subgroup effects, with one exception: the reduction in mean to complete resolution of pain was greater with intramuscular...*). Also, added below line to the results text where the subgroup effect is reported.

“However, the effect modification is suggested by comparison between rather than within studies.”

## ***Authors' Reply to the reviewers Comments***

Reviewer: 1

Comments

**This is a very detailed review on the use of corticosteroids in sore throat. The possible adverse effect of gastrointestinal bleeding still seems to be a problem in the use of corticosteroids for pain relief in sore throat.**

Gastrointestinal bleeding is probably a concern in patients who take higher doses of corticosteroids for a longer period of time in patients who are critically ill or have other risk factors. However, in this context where very low doses (20mg) were given once, we do not believe that this is an issue (see <http://bmjopen.bmj.com/content/4/5/e004587.short>). We examined adverse effects and gastrointestinal bleeding was not reported to have occurred in any of the patients included in our meta-analysis. We have reworded our manuscript extensively to come to a more cautious conclusion about adverse effects, as stated above.

**Lozenges containing flurbiprofen may be a good alternative to corticosteroids for sore throat pain.**

We agree with the reviewer that lozenges and other therapies are alternatives and/or adjunctive therapies that might be considered and are routinely used. We do not discuss these in detail because it is out of scope for our review, but note that patients would have received steroids in addition to usual care in these RCTs.

**The manuscript may be accepted for publication as it is.**

Thank you for the kind review.

Reviewer: 2

Comments

**We commend the authors on a very well written and rigorously researched manuscript that may have important implications on the treatment of sore throats using corticosteroids.**

**I think there are few things that require some clarifications that would strengthen this manuscript.**

- 1. The value of any intervention (i.e. steroids in this case) must balance benefits and potential harms. The meta-analysis of RCTs does a nice job of summarizing potential benefits of steroids in this situation. Although the authors also summarize harms from each study, it is well known that harms of interventions are often poorly ascertained by RCTs for several reasons. It would be worthwhile for authors to note possible under-ascertainment of harms in the discussion and supplement with any data re: harms from observational studies in this patient population.**

Thank you. We agree and now state:

“There was no increase in the few serious adverse effects in the included RCTs, although patient-reported minor adverse effects might not have been captured. Further, potential adverse effects that have a longer lead time, are more likely to occur after repeated use, or are serious but very rare would not have been captured in the RCTs.”

Our conclusions have been modified accordingly.

**2. The authors include one reference #33, which recently evaluated harms of steroids using a large database; however, they minimize the impact of these results, citing concerns of confounding by indication, differences in doses, and differences in duration. While some of these are valid concerns, it should be noted that the concerns about confounding by indication were recently addressed by recent letter to editor. If authors agree with rebuttal, they might use data from this study as one observational study to report steroid harms.**

The study referenced has garnered a lot of attention about the possibility of short-term steroids (at doses and durations much longer than are used in this context) might increase the risk of fractures, VTE, and sepsis. Thank you for referring to the rebuttal by the authors online, which states “The self-controlled case series (SCCS) design is very powerful in controlling for underlying comorbidities in a patient. If there are immediate changes in the patient’s underlying comorbidities at the time of the prescription, then there would be a concern.”

The timing of steroid prescription is critical – patients would have been prescribed steroids at a time that they either i) had an acute illness, or ii) a deterioration in an underlying chronic disease. For this reason, the “self-controlled case series” is inappropriate for detecting adverse effects.

The authors of this reference also performed a case-control study by indication according to very broad categories (e.g. “back problem”) and report the results in the appendix. Unfortunately, no attempt was made to control for confounders such as aetiology, severity of illness, age, etc.

Although we do not find the results of this particular study compelling, they cannot be dismissed altogether. We acknowledge this evidence in the discussion by saying:

“Recent observational studies have raised the possibility of extremely rare but serious adverse effects following short courses of corticosteroids. The quality of this evidence is, for a number of reasons, very low with respect to the question at hand. The studies use observational designs from large data bases with suboptimal verification of diagnoses; serious confounding by indication raising the possibility that the association is a result of the underlying disease process (e.g. acute inflammation or exacerbation) rather than the corticosteroids themselves; and indirectness in that the doses used in the sore throat RCTs are lower, and the duration considerably shorter, than those used in the observational studies.”

**3. As pointed out by the authors, there were significant biases associated with many studies. Given this limitation, conclusions of benefits should likely be more tempered.**

Thank you. We have tempered the conclusions throughout the manuscript based on concerns of adverse effects, as noted above in our response to the editors.

**4. The  $I^2$  for most outcomes suggested significant statistical heterogeneity, which makes pooling of results difficult to interpret. Authors could further evaluate this heterogeneity with sensitivity analyses to see if this could reduce heterogeneity. This should also be discussed as a limitation of the meta-analysis in the discussion section.**

As you mentioned, we observed considerable statistical heterogeneity in most of the outcomes. To explore source(s) of this heterogeneity we performed subgroup analyses and reported the results for each outcome. We rated down for inconsistency in some the outcomes due to the observed unexplained heterogeneity and in outcomes that we decide not to rate down, the clinical inconsistency was deemed as not important, following GRADE methodology, since all the results of included studies have similar clinical implication. We agree with you that the unexplained statistical heterogeneity should be mentioned as a limitation in the discussion section and added below text to the list of limitations in the third paragraph of discussion on page 10.

“We observed substantial statistical heterogeneity in some of the outcomes. We explore the source(s) of heterogeneity by subgroup analysis and rate down for inconsistency in GRADE assessments for outcomes with unexplained heterogeneity unless the results of all included studies had similar clinical implication.”

**5. The quality assessment and limitations (both within-study and between-study) should be expanded, as this is one of the most important aspects of a meta-analysis.**

The limitations of the review are discussed in the third paragraph of the discussion. The quality assessment in terms of within study (risk of bias assessment) and between study (heterogeneity and inconsistency) are presented in detail in the results section (table 1, table 2, and supplement file related to the details of risk of bias in individual trials).

We have also added below sentence as part of discussion to expand on limitations of included trials reporting adverse events:

“There was no increase in the few serious adverse effects in the included RCTs, but none reported potentially important patient-reported adverse effects such as insomnia or mood changes. Further, potential adverse effects that have a longer lead time, are more likely to occur after repeated use, or are serious but very rare would not have been captured in the RCTs.”

**6. Emphasize the need for high quality data to show true value on this topic.**

Thanks for your comment; we added below text to the end of the discussion.

“More high quality data would be helpful to fully understand the balance of benefits and harms according to symptom severity, especially in primary care settings.”

#### **Minor comments:**

**1. On page 3 the hyperlink to MAGICapp appears to be user protected. May consider mentioning that or reference it in the reference section.**



The link to access to the guideline public page is not yet publicly available as the guideline is not published yet and is under review at the same time by the BMJ; it will be available as soon as the guideline gets published. However, you have access to the guideline manuscript as a supplementary file to this manuscript.

**2. In Table 1, Hayward should be associated with Reference 14 not reference 4.**

Thanks for pointing out our mistake. The reference number is corrected.

Reviewer: 3

Comments

- **Essentially this is an update to the systematic review of the same name published in the BMJ and later in the Cochrane Library, with last update on October 2012. Since this publication, one large new RCT has been published. The introduction states that this review is part of a new program from a commercial group called MAGIC, and has apparently already been published as a guideline (though I was not able to access the link on Line 47), so perhaps this is still to occur.**

Thanks for your comment. The guideline is not published yet and is under review at the same time by the BMJ; the link will be will be accessible as soon as the guideline gets published. However, you have access to the guideline manuscript as a supplementary file to this manuscript.

- **The manuscript uses typical systematic review methods to search for, select and synthesize eligible trials. The authors performed a bridging search from 2010 to present, and identified the one new trial (Hayward et al) as noted above. However, I note that the authors also identified a trial of Ahn et al 2003 which had been identified and excluded as not being eligible in the Cochrane review. This raises 2 questions, first how was this paper identified if the current manuscript's search only extended back to 2010? I don't see from their methods section that this trial could have been picked up. Second, the Cochrane review authors excluded this paper as it was not a randomized controlled trial. While I have only access to the English abstract of this Korean language paper, this states "The 109 patients were arbitrarily divided into 3 groups and each group was prescribed different combinations of oral steroid and NSAIDS." It is unclear to me how this previously excluded paper would have been identified, and why it would have been included? Did the authors find out additional information from the authors that this was indeed an RCT?**

As mentioned in the methods section, we reviewed reference lists from relevant reviews for additional eligible trials. In our searches we found two systematic review of randomized trials<sup>13 14</sup> that included Ahn 2003 trial. The article was in Korean language and we asked a Korean language colleague to make sure this is a randomized trial. We also double checked information using as online translator to make sure the study is a randomized trial (see also our reply to the editor above, on page 4) . The Korean article full-text is available here:

<http://www.kjorl.org/journal/view.php?number=2530>.

- **In the discussion section the authors noted that inclusion of the 2 “new” papers doubled the number of participants. In fact it was really only the Hayward et al trial which added substantial numbers to this, the small Ahn study (which likely should not have been included) added 72 patients. Certainly the Hayward paper adds considerably to the systematic review, both in numbers of participants, also the setting ie general practice, and the use/not use of concurrent antibiotics. These latter aspects were indeed why the Hayward trial was justified.**

We would like to thank you for the comment and noting the ingenuity aspects of Hayward et al (2017) trial. We mentioned that we included two new articles because we decided to update the recent Cochrane review and compared to that we had two additional trials. The reason for excluding the Ahn et al (2003) from the Cochrane review is not clear for us as two other published systematic reviews of randomized trial published in 2010 and 2013 found this study eligible.<sup>13 14</sup> We have explained above why we think the Ahn trial is eligible for this review.

- **I am unclear what the value of the patient panel was to this study. In the discussion it claims that the panel considered additional outcomes that the participating patients considered important including recurrence, or days missed from school or work. However, some of these outcomes were clearly listed in the Cochrane review – in what way therefore did the patient panel change the planned methods?**

The patient panel members did not identify any additional benefit outcomes that were not captured by the Cochrane review. Involving patients in the process gave us additional confidence that the outcomes we chose were appropriate and important. In our experience, this is the first time (of seven completed or ongoing Rapid Recommendations) that the patients did not identify additional outcomes of importance or identify outcomes that were not important to them that had previously been included. Therefore, this confirmation is important.

The patient panel members added additional value by helping to interpret the results. For example, they felt that the benefits (although modest) would be sufficiently important and that the harms (although evidence is not high quality) sufficiently minor that many patients would choose to use corticosteroids.

- **The conclusions of the study, final paragraph, seem to make generalizations not supported by the evidence. ‘many patients are likely to consider them important’ – what is the basis for this statement? And that ‘adverse effects are rare or absent’ - again would agree for the ‘serious adverse effects’ part of this sentence, but there is evidence of adverse effects of steroids so these statements do not quite seem correct.**

We have modified the concluding paragraph accordingly: the comment that ‘adverse effects are rare or absent’ has been removed. We have confidence that many patients will likely choose to use corticosteroids, in part by the patient panel member’s assessment of the evidence as discussed immediately above.

The conclusion now reads:

“Although the benefits are relatively small, many patients are likely to consider them important. However patients with less severe sore throat will glean less absolute benefit from corticosteroids. Thus the balance of risks and benefits almost certainly depends on the severity of the patient’s sore throat. With available evidence suggesting that serious adverse effects are very rare or absent, the addition of one or two doses of steroids to the symptomatic management of sore throat is likely to appeal to many patients. More high quality data would be helpful to fully understand the balance of benefits and harms according to symptom severity, especially in primary care settings.”

- **I guess the question is whether the addition of a new trial justifies a new protocol, review process and publication? Certainly the new large trial is important for this area and reduces summary effect size, while increasing generalizability to primary care settings. The authors don’t really comment also on the issue of how readers should interpret the findings of a systematic review when a large well conducted (essentially negative) new RCT trial has somewhat different findings from the smaller (more methodologically flawed) studies that showed a small significant effect - what should the clinician ‘trust’ the most here?**

The reviewer highlights the purpose of systematic reviews and meta-analyses, which aim to interpret the whole body of evidence when on the surface some studies might appear to be conflicting (e.g. some statistically significant, others not). In this case, the new large and well-conducted study was consistent with the “smaller (more methodologically flawed) studies”, despite the fact that not all of the outcomes reached statistical significance on their own in the new study. In our meta-analysis, we used the GRADE approach and explicitly considered inconsistency between studies as well as risk of bias (methodological quality). In general, the evidence was consistent across studies, including the new trial, in suggesting modest benefits with corticosteroids.

- **Some minor typos - the included author Kiderman is misspelt throughout (as Kinderman), and the year of the O’Brien 1993 paper is incorrectly noted as 1994 . This link did not work <https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn>**

Thanks for pointing out these issues. The mistake on Kiderman 2005 and O’Brien 1993 are corrected in the text and tables. As the guideline is not yet published and is under review at the same time by the BMJ, the link is not yet accessible; it will be available as soon as the guideline gets published. However, you have access to the guideline manuscript as a supplementary file to this manuscript.

Reviewer: 4

Comments

## 1. GENERAL COMMENTS

**This meta-analysis from B. Sadeghirad and coworkers on “Corticosteroids for treatment of sore throat provides an important level of evidence (Ia) and clear recommendations for the use of single low (up to 10mg) doses of systemic corticosteroids to treat sore throat in the context of acute tonsillitis, pharyngitis and the sore throat syndrome in children older than 5 years and adults. The overall and subgroup analyses are well done and the conclusions and recommendations based on the studies analyzed in the meta-analysis.**

Thanks for your comment.

## 2. COMMENTS ON SPECIFIC SECTIONS

### Abstract

**- Page 2 (Results). The maximal dose of steroid (10mg) should be identified here (line 31). The last sentence “None of the ...” is too categorical since some adverse effects have been reported in the different studies. It should be softened by something like “probably”.**

Thanks for your comment. We added the route of administration and maximal dose of most commonly used intervention. We also revised the abstract results section to reflect your comment on adverse events.

[“None of the included studies reported serious adverse effects attributable to treatment.”](#)

**- Page 2 (Conclusion). A meta-analysis cannot provide cause-effect conclusions but recommendations. Thus, the word “provide” should be changed by, for example, by “is recommended”.**

Thank you for your comment. We respectfully disagree with the reviewer. We believe that randomized trials provide empirical evidence that allows cause-effect inferences. When the trials are at low risk of bias without problems with imprecision, inconsistency, indirectness and publication bias the inferences can be strong (high quality evidence). Systematic reviews of randomized trials provide stronger evidence of cause-effect relationships than individual randomized trials. These inferences may get stronger yet when appropriately pooled in a meta-analysis.

Moreover, it is generally not the purpose of a systematic review to provide recommendations, but to synthesise and appraise the evidence. The companion guideline in this provides the recommendation issues by the panel based on this systematic review.

## • Methods

- **Page 6 (lines 7-17). It looks like all larger effects in the subgroup analyses are significant when only “parenteral versus oral” (Appendix 4) is significant. This should be clarified. It is clearly stated in the discussion section (page 10, lines 52-54)**

The decision about subgroup analyses and the direction of the effects were made a priori and published in the registered protocol before data extraction and data analysis. The PROSPERO protocol is available here: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42017067808](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017067808). We have also revised the text in the results section as per reviewers’ suggestion to reflect more details on subgroup analysis.

## • Results

- **Page 7 (lines 17-20). The identification of studies concerning age of participants is not correctly reported (see Table 1): 5 studies are in adults, 3 in children, 1 in both children and adults, and in one the age is not reported. This should be also clarified.**

Thanks for pointing out this issue. We revised both table 1 and the results text to reflect the correct distribution of included trials.

The results now say:

Three studies enrolled children,<sup>8 10 11</sup> six studies adults,<sup>3-5 7 9 12</sup> and one study included both children and adults.<sup>6</sup>

Also, in table 1, the average age is added to the relevant column.

- **Table 1 (page 14). In the “dose and duration” column, the box for Betamethasone should report the real dose, in addition to the administered volume.**

The actual dose used in the study is not reported but we added the dose based on best guess from US formularies.

- **Table 2 (page 15). In the “Absolute effect estimates” column, the MD values in the boxes for “Mean time to onset ...” and “Mean time to resolution ...” should be better presented with a negative value (-) to avoid confusion with the Forest plots in Figures 4 and 5, respectively. In the footnote 5, “now” should be changed to “one”.**

Thanks for your comment. We revised the footnote text. In table 2, to reflect the direction of the effect for continuous outcomes such as mean time to onset of pain relief or resolution of pain we provided adjectives such “fewer”, “higher”, or “lower”.

**- Figure 1 (page 21). The main reasons of drop-outs in the box “Articles excluded (N=2303) should be reported”.**

We added main reasons for excluding title/abstracts in figure 1.

**- Figure 6 (page 26). If the reported reduction of pain is “at 24h” this time should be reported in the figure legend.**

We added the suggested text to the figure legend.

**- Appendix 3 (page 31) and 4 (page 32). In the P value column, the symbols “ \*\*\* ” or “ \*\* ” for small number of trials is confusing since asterisk are usually used for p values. Could they be changed to some kind of abbreviation defined as a table footnote (SNT, small number of trials)**

We change the asterisk with difference symbol to avoid the confusion.

#### • Discussion

**- Page 10 (lines 19-24). The word “reduce” denotes cause-effect. OR / RR from meta-analysis do not provide cause-effect data (this is only given by RCT studies) but association data. All word denoting cause-effect should be changed all over the document (also in page 11, line 44, and in the footnote 13 of Table 2).**

Thanks for your comment. We respectfully disagree with the reviewer. The reviewer seems to say that individual RCTs yield stronger inferences regarding cause-effect than meta-analysis of all the RCTs available. If this were true, we should not bother to try and aggregate results across RCTs. As above, the evolution of summarizing evidence over the last 30 years is on the basis that considering all RCTs together and using statistical techniques to pool results allow stronger cause-effect inferences than do individual RCTs. We have therefore not modified the text.

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