Reviewer’s report

Title: Vibration of effects from diverse inclusion/exclusion criteria and analytical choices: 9,216 different ways to perform an indirect comparison meta-analysis

Version: 0 Date: 29 May 2019

Reviewer: Ersilia Lucenteforte

Reviewer's report:

The paper by Palpacuer et al. is on the Vibration of Effect (VoE), a method to "systematically evaluate the breadth and divergence" of the results.

The method consists in computing the distribution of point estimates of Effect Sizes (ESs) and their corresponding p-values under various analytical scenarios defined by the combination of different methodological choices. When ES is in the opposite direction between the 1st and the 99th percentiles, there is "Janus effect" indicating the presence of substantial VoE. The method has been described in observational epidemiology, has been less explored in classic meta-analyses and never used (it is right?) for network meta-analyses (NMA)

Authors used a controversial NMA as case study: comparison of nalmefene and naltrexone in the treatment of alcohol use disorders.

VoE could be the right way to study the common recurring theme of discordant meta-analyses.

One of authors of the paper by Palpacuer et al. authored the two nicely papers quoted as methodological paper for VoE methods [16, 96] and this represents a strength.

I was really happy in reviewing this paper I found very nice, well designed and well written. I only have few suggestions

1. The search was limited to clinical trials (pag. 5, line 48/49)

Most NMA published to date incorporates data from randomized controlled trials (RCTs) only; however, inclusion of non-randomized studies may sometimes be considered especially when the endpoint of NMA is drug safety. Non-randomized studies can complement RCTs or address some of their limitations (short follow-up time, small sample size, highly selected population, and high cost).
The case study used by Palpacuer et al. is not the right example to study how the inclusion of non-randomized studies influences the VoE, because is an efficacy meta-analysis. However, authors could address the effect that non-randomized studies could have on VoE.

2. The search was updated in August 2017 (pag. 5, line 48/49)

I suggest to update the search. I don't think this is an hard work because I performed a quick search in pubmed and I found very few papers. The updating is just a formality.

3. Authors computed the distribution of ES and corresponding p-values considering the combination of various methodological choice (pag 6, lines 49-54 and Table 1).

I found the statistic choices very few. For example, many NMAs published to date use Bayesian approach and author did not evaluate Bayesian versus frequentist approach.

4. Authors described two meta-analyses with contradictory results in the Appendix (pag 6, line 56-58). I found the description very useful if performed on all discordant meta-analyses. Could they describe characteristics of all discordant meta-analyses in the main text? It is possible to have an indication on the most important methodological choices that influence the discordance?

5. Authors found Janus effect for indirect comparison of nalmeffene to naltrexone (fig 2, 3856 combinations) and for direct comparison of nalmeffene to placebo (fig 4, 86 combinations), and no Janus effect for direct comparison of naltrexone to placebo (fig 3, 1988 combinations).

Are the comparisons of nalmeffene to placebo and naltrexone to placebo mixed or direct?

6. The VoE method has been described in observational epidemiology but has been less explored in meta-analysis (pag 10, lines 34-36). For the readers it would be important to know how often the method has been used and what is the "prevalence" of Janus effect in medical literature.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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