Reviewer’s report

**Title:** Antihistamine Effects and Safety of Fexofenadine: A Systematic Review and Meta-analysis of Randomized Controlled Trials

**Version:** 3  **Date:** 08 Jul 2019

**Reviewer:** Jiraganya Bhongsatiern

**Reviewer's report:**

Thank you for allowing me to review this original research article three times. The results and discussion sections were somewhat complicated as the comparisons were not straightforward; I spent many hours trying to generate useful suggestions to the authors. The objectives of the study are clearly described, and I agree with the authors’ claims that a collective evidence of the antihistamine effects and safety profiles of fexofenadine comparing with other first- and second-generation antihistamine drugs and placebo were lacking. The results and conclusions are still confusing, and I would like to urge the authors to carefully paying attention to this part.

Main comments: Results and Discussion sections - I think it is reasonable to mention that the antihistamine effects (the inhibition rate of histamine-induced wheal and flare) of fexofenadine were significantly higher than that of placebo and were not significantly different compared with the second-generation antihistamines (Figures 2 and 3). The heterogeneity of the analyses was questionable. Nonetheless, the inconsistent doses and types of the second-generation antihistamines were demonstrated in the study and indeed was the limitation of the study.

The safety part; however, was confusing to me. The authors concluded that fexofenadine has better safety profiles when compared with the second-generation antihistamines. From the study, the AE frequency, change of CFF, change of CRT were reported no difference (Figures 4b, 6b, and 7b, respectively), while the significantly lower sedative frequency, less change of CTT, and less change of LARS were also reported (Figures 5b, 8b, 9, and S9, respectively). Given no results of the change of VAS of drowsiness between fexofenadine and the second-generation antihistamines, it is difficult to conclude that the fexofenadine has arguably better safety profiles. The author pointed out that sedative effects is one of the most concerned issue of AE, but we cannot rule out the fact that the change of VAS of drowsiness cannot be analyzed and the results of the overall cognitive/psychomotor function were inconsistent to favor fexofenadine over the second-generation antihistamines. I think the authors should carefully discuss this disagreement than concluding the better safety profiles of fexofenadine than the second-generation antihistamines. It might be worth to try to construct a table to summarize the results for the audience to quickly understand the discrepancy demonstrated in the result context.

Other comments are about grammatically errors and formatting which I think the authors should not ignore. The followings are a couple of points to consider but I would suggest the authors to carefully review the edits to avoid any simple mistakes on writing.
(1) Results section, Publication Bias, Page 10 line 14-20: Please specify the Figure numbers (Fig. S11-Sxx) and (Fig. Sxx-S19).
(2) Spelling - Results/ Search Results, Page 7 line 20: Participants not participants; Page 7 line 23: Notably not notably; Discussion, Page 11 line 7: arrhythmia not arhythmia, Conclusions and abstract, Page 1,4, 12: unprecedented not unprecedent.

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.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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