Author’s response to reviews

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

Authors:

Cheng-zhi Huang (15626044356@163.com)
Zhi-hui Jiang (jandsphy@163.com)
Jian Wang (13889909318@139.com)
Yue Luo (15622720399@163.com)
Hua Peng (doctorpeng2006@hotmail.com)

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Response letter

Technical Comments:

Editor Comments:
Please consider the reviewers’ suggestion carefully, before resubmitting. These are essential revisions. BMC Pharmacology and Toxicology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Thank you very much for your reminder! Below we have carefully replied to the comments of two reviewers.

Reviewer reports:
Emanuel Raschi (Reviewer 1): There are two remaining (minor) essential issues:
- the word "unprecedented" in the conclusion of the abstract is too strong and cannot be drawn considering limitations: data mainly from healthy subjects, old studies with low-to-moderate quality, high heterogeneity in some circumstances (the fact that a manuscript published in the Lancet draw certain conclusion in the presence of high heterogeneity cannot be used as a standalone criterium to support the authors' conclusion). The authors themselves used the word "probably" in the previous statement. Please align the abstract to the full text (beginning of the discussion).
Thank you very much for your suggestion! We have changed the statement to “Fexofenadine probably has an excellent safety profile”.

Figure S20 does not appear to be quoted in the text. I can only see that, in the results of the publication bias, the term "Sxx" is used. Please check.

Thank you for your reminder! We have added figure S20 to figure 5b (see Fig. 5b) and added the information (Fig. S11-S19) to the revised manuscript (see Results section, Publication Bias, Page 8 line 17-11).

Jiraganya Bhongsatiern, PhD (Reviewer 2): 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.

Thank you very much for your review! We greatly appreciate your time, patience, effort and professionalism.

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.

Thank you very much for your suggestion! We have added your statement “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” to the discussion part (the first sentence) of the revised manuscript.

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.
Thank you very much for your suggestion! Even though sedative effects is one of the most concerned issue of AE, we can’t ignore the fact that no literature was analyzed for the change of VAS of drowsiness. For this reason, we would like to add “more likely” to the sentence “fexofenadine more likely has better safety profiles when compared with the second-generation antihistamines”. To clarify the result, as you suggested, we have also constructed a table to summarize the results including the antihistamine effects and safety profiles (Table 2). Please check it in the revised manuscript.

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.

Thank you very much for your suggestion! We have carefully reviewed the revised manuscript and corrected those mistakes.