Author’s response to reviews

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

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Author’s response to reviews:

Response letter

Technical Comments:

Editor Comments:

Dear Authors,

the response to the reviewers’ queries are very much appreciated, since they have significantly improved the manuscript. However, there are some remaining points that need your attention. Without these revisions, the manuscript cannot be accepted because the main concern is that data do not fully support general conclusions on the better safety profile of fexofenadine.

Reviewer 1 - QUESTION
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).

ANSWER
Thank you very much for your suggestion! We have changed the statement to “Fexofenadine probably has an excellent safety profile”.

EDITOR
The submitted manuscript only partially addresses the concern:
The word “unprecedented” seems to be maintained in the online abstract, which should be identical to the abstract contained in the submitted manuscript. The conclusions must be revised in any case (see below).

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

Reviewer 2 - QUESTION
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.

ANSWER
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.

EDITOR
The submitted manuscript only partially addresses the concern. While the addition of table 2 certainly helps to clarify the issue, as clearly indicated by the reviewer the results of the overall cognitive/psychomotor function were inconsistent to favor fexofenadine over the second-generation antihistamines.

Accordingly, the statement “Fexofenadine probably has an excellent safety profile, which is more likely better than that of the first-generation antihistamines, especially in sedative effects and cognitive/psychomotor function compared with the second-generation antihistamines” remains confusing and not supported by data. Therefore it cannot be accepted.
The Authors must revise this sentence both in the abstract and in the conclusions since fexofenadine has a better safety profile only when compared to first-generation antihistamines. When compared to second-generation antihistamines, the lack of data on VAS of drowsiness does not allow to draw firm conclusions, although some presently available evidence on cognitive/psychomotor function favours fexofenadine. The wording “excellent safety profile” must be avoided.

Thank you very much for your suggestion. We have revised the improper statements both in the abstract and in the conclusions part. Please check them in the revised manuscript.