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:
This revised version does not fully respond to the concerns expressed by referee 1. It is necessary to clarify also the point raised by referee 2.

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

Reviewer reports:
Emanuel Raschi (Reviewer 1): The authors revised the systematic review, by proving data on population (actually healthy volunteers), risk of bias (low/uncertain), and funnel plots.
The conclusion remains a major concern. In their rebuttal letter, the authors reply that heterogeneity is low when comparing fexofenadine with second-generation antihistamines; however, this statement does not appear to be supported by the data presented in the text (99% of heterogeneity for efficacy, figures 2 and 3; 79% in figure 6b; 76% in figure 7b; 96% in figure 9b). The heterogeneity on sedative effect (a key conclusion) is not shown in figure 5b, and odds ratio is largely driven by a single study
Thank you very much for your review! In our last rebuttal letter, we double checked that we actually not mentioned heterogeneity is low when comparing the antihistamine effects of fexofenadine with those of the second-generation antihistamines. However, we mentioned “A few of the 51 included studies compare the antihistamine effects and other safety profiles of fexofenadine with other antihistamines and placebo, the heterogeneities are very high. Most of the 51 included studies compare the adverse events frequency and sedative effects frequency of fexofenadine with other antihistamines and placebo, the heterogeneities are low” in our response to questions in the “DISCUSSION AND CONCLUSION” part of our last rebuttal letter.

The heterogeneity information of figure 5b is shown in Fig. S20. Since reference Howarth1999 weighs a lot for the odds ratio, we carefully read this reference to see if any abnormal factors resulted in the relative high event rate, unfortunately, this reference is perfect for the inclusion criteria. Actually, the result could be changed even if we eliminate this reference.

Taken together, these data on healthy volunteers do not allow to draw the conclusions stated by the authors in the abstract and in the full text. the first sentence in the discussion should be also corrected ("Our meta-analysis indicates that fexofenadine has positive antihistamine effects and safety profile in patients with indications requiring antihistamines").

As suggested in the first revision, this systematic review highlights the need to perform well-designed head-to-head studies in people with therapeutic indications requiring antihistamines.

Thank you very much for your review! We can easily find reference (such as ref 1) with high heterogeneities and relatively certain conclusion. However, we do agree with your opinion that certain conclusion can’t be drew with high heterogeneity. Therefore, we have added a word “probably” to describe the uncertain conclusion which was contributed by the high heterogeneities. Please check these sentences in the abstract and in the full text of the second revised manuscript.

Reference

Jiraganya Bhongsatiern, PhD (Reviewer 2): The authors have provided good responses with adequate references to reviewers' comments. A minor point I would like the authors to improve the manuscript by adding the following information.

1) Please include the placeholders of supplementary materials Fig. S11-S19 in the context. They could also be in the discussion section. This would help lead the readers to the Funnel plot as stated in the method section.

Thank you very much for your review and suggestion! We have added one paragraph describing the publication bias and the placeholders of supplementary materials Fig. S11-S19 to the end of the RESULT part.