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:
When revising the manuscript consider very carefully suggestions provided by Reviewer #1: in particular, overall findings (very high heterogeneity, both statistical and clinical, together with high risk of bias) do not allow to draw firm conclusions on the efficacy and safety of fexofenadine, especially in comparison with second-generation agents.

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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): This systematic review analyzed 51 RCTs (as of January 2018) comparing fexofenadine with placebo or other first- and second-generation antihistamines, for efficacy and safety (adverse events, sedative effects, cognitive/psychomotor function). They performed standard meta-analytical approach and found that fexofenadine has a positive antihistamine effect (no worse
than second-generation agents) and a better safety profile as compared to first-generation drugs and second-generation medications (for sedative and cognitive/psychomotor function). The following major issues require authors' consideration:

- STUDY CONCEPTION. The authors performed this study due to the lack of systematic review. However, this cannot be formally considered as a scientific reason: systematic review with meta-analysis are carried out when conflicting evidence exist, increase statistical power (individual studies were underpowered) or to address safety/efficacy issues not primarily covered by individual studies. Therefore, scientific rationale and study aim should be clarified.

Thank you very much for your review and suggestion! We do agree with your opinion. We improperly followed some writing styles of meta-analysis. As you stated, we have corrected our study aim as “However, there is still a lack of collective evidence regarding the antihistamine effects and safety profiles of fexofenadine relative to other antihistamine drugs and placebo.”

- METHODS. It is unclear if search and analysis of unpublished data were also undertaken (see paragraph "search strategy", last sentence). Moreover the authors stated that funnel plot was performed, but no results are provided.

Thank you very much for your review! For the unpublished data, we meant the RCTs in The Cochrane Central Register of Controlled Trials (CENTRAL) that had been registered and had results but not been published in the literature. We searched these trials but none of them were included. To reduce readers' confusion, we have rewritten that sentence as "References of included studies and additional sources were examined to reduce the search bias."

We performed the funnel plot but we didn’t provide in the manuscript due to our concern of pages constraint. We have provided it in the supplementary material.

- RESULTS. Here there are different aspects to be carefully addressed. First, very high heterogeneity (sometimes reaching 100%) emerged in almost all analyses performed on fexofenadine vs second-generation agents (i.e., the analyses that bring clinical implications for prescription). The authors stated that inconsistent doses and different type of antihistamines might cause this statistical heterogeneity. However, also clinical heterogeneity exists, because of the different therapeutic indications (allergic rhinitis, allergic asthma, chronic idiopathic urticarial). Additional (sensitivity) analyses are required to verify this issue and offering an additional clinical perspective. Second, risk of bias analysis highlighted several major concerns. Figures might be useful to fully provide data especially because a high/uncertain risk of bias emerged for allocation concealment and blinding of outcome assessment. My proposal is to provide one figure summarizing all studies according to the different biases, and one supplementary figure to detail specific biases of individual studies. results revisited. Do the authors perform sensitivity analysis according to the quality of studies? Overall, results are very rich of data and the authors should attempt to convey the reader towards key findings. For instance, I would make a selection of the figures, by identifying those more clinically useful (e.g., fexo vs second-generation drugs) to be presented in the full text, and those of secondary/marginally importance as supplementary material (e.g., fexo vs placebo)

Thank you very much for your suggestion! Regarding to the high heterogeneity, as you stated, it’s not only caused by inconsistent doses and different type of antihistamines but also by different therapeutic indications. We would like to analyze how much does different therapeutic indications contribute to heterogeneity. First, for the comparison of antihistamine effects and cognitive/psychomotor function
(CFF, CRT, CTT, LARS and VAS of drowsiness), participants in these studies actually were all healthy volunteers (we omitted this important information in the manuscript), so no indication was involved in this part. Second, for the comparison of adverse events frequency and sedative effects frequency, no need to analyze because very low heterogeneity exists.

As to risk of bias, according to your suggestion, we have provided one figure summarizing all studies according to the different biases and another figure to detail specific biases of individual studies in the supplementary material. As shown in Fig. S1, for allocation concealment, 22% of included studies had low risk of bias, 78% had unclear risk of bias. For blinding of outcome assessment, 27% of included studies had low risk of bias, 73% had unclear risk of bias. It’s hard to rank the quality of these studies with high percentage of unclear risk of bias, what we can do is to perform sensitivity analyses by eliminating the included studies one by one.

According to your suggestion of selecting key findings (more clinically useful (e.g., fexo vs second-generation drugs)) in the text, we have rewritten the results part, please check it in the revised manuscript.

- DISCUSSION AND CONCLUSION. These sections should be substantially revisited according to the aforementioned comments. In my opinion, the high heterogeneity together with the substantial risk of bias make results very uncertain in terms of reliability. The conclusion that fexo is no worse than second-generation antihistamines for efficacy and even better in terms of safety is not justified. Based on these findings, this systematic review highlights that there is need to perform well-designed head-to-head studies.

Thank you very much for your suggestion! We do agree with your opinion. The conclusion that fexofenadine is no worse than second-generation antihistamines for efficacy and even better in terms of safety should be carefully drew due to high heterogeneity and unclear risk of bias. 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, so we think the conclusion that fexofenadine is better than the second antihistamines in terms of the adverse events frequency and sedative effects frequency has a great possibility. 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. It’s hard to perform subgroup analysis because no more than 6 studies were included in each one comparison and many differences exist among studies. Sensitivity analyses also were conducted by eliminating the included studies one by one to reduce the heterogeneity, which were unsuccessful. Based on these limited data, more well-designed head-to-head studies are needed.

We have modified some descriptions of our conclusion according to our above statement. Please check it in the manuscript.

Jiraganya Bhongsatiern, PhD (Reviewer 2): This is a systematic review and meta-analysis of 51 randomized controlled trials (RCTs) to quantitatively examine antihistamine effects and safety of fexofenadine, a selective H1 antagonist. The authors performed an electronic literature search of 841 records total and selected 51 studies of 14,551 participants (healthy subjects and patients with allergic diseases) to further conduct meta-analyses to compare fexofenadine with either other antihistamines (both the first and second generations) or placebo. The outcome measurements for antihistamine effects include inhibition rate of histamine-induced skin wheal and flare. The safety measurements were assessed by adverse event (AE) frequency, sedative effect frequency, and the change of
cognitive/psychomotor function scores. Five cognitive/psychomotor function scores were used: critical flicker fusion (CFF), choice reaction time (CRT), compensatory tracking test (CTT), line analogue rating scales for sedation (LARS), and visual analogue score (VAS) for drowsiness. The risk of bias and methodological quality was also evaluated.

From my perspective, this study is good with minor edits. The study demonstrated sufficient results of positive antihistamine effects and safety profile of fexofenadine which mostly are in agreement with other published studies. There were some inconsistencies which, after sensitivity analyses, the authors suggested they were owing to differences in dose, duration and wash out periods among studies. As a consequence, two studies were excluded in the assessment of antihistamine effects. This part was acceptable.

Thank you very much for your review and suggestion!

The minor edits that I would like to suggest the authors to modify are the followings:

1) Background, Page 4, line 8: "As such, the aim of this study was to analyze…", not "analysis".

Thank you very much for your review! We have corrected the “analysis” to “analyze”. Please check it in the manuscript.

2) Background, Page 3, line 45: "Symptoms such as itching, sneezing, rhinorrhea, and rhinobyon caused by … [2]". The authors may want to double-check the word "rhinobyon". I think it does not belong here. Please check.

Thank you very much for your suggestion! We have deleted the “rhinobyon”.

3) Results, Page 8, line 17: "Four studies compared with the second-generation antihistamines, as shown in Fig. 7(b), the change of CRT (WMD = 5.28…). This sentence was incomplete. Please check.

Thank you very much for your review! We have added some information in this sentence as: “Four studies compared with the second-generation antihistamines [15,28,49,59], as shown in Fig. 7b, the change of CRT were not different (WMD = 5.28; 95% CI: -3.07 to 13.63, P = 0.22)”.

4) Table 1 "Characteristics of included studies", please double-check the total number of participants in each treatment arm.

For example, reference #57 Larbig 2006 published the randomized, double-blind, three-treatment, three-period, single-dose, cross-over study comparing levocetirizine, fexofenadine and placebo. The study also stated that thirty subjects were randomized. I think it is not accurate to report n=30 for each treatment arm.

Moreover, there was no treatment arm of levocetirizine reported for this reference (#57) and it was included in meta-analyses to only compare fexofenadine and placebo, not between fexofenadine and levocetirizine (2nd generation antihistamine). I think it is more accurate to at least discuss the reason of why the authors did not include the comparison between fexofenadine and levocetirizine in the analyses.

Thank you very much for your review! Reference #57 Larbig 2006 is a cross-over RCT, in fact, three was no agreement on what’s the sample size in cross-over RCT for meta-analysis. Some meta-analysis references used the number of each treatment arm (n) in the first part of cross-over RCT as sample size, some meta-analysis references used 2n as sample size. In general, more high-impact references used n as sample size, which is the reason why we decided to choose n as sample size in the cross-over RCT.
Many references[1, 2, 3] and also clinicians in China consider levocetirizine, fexofenadine, desloratadine as the third generation antihistamine. So we followed this classification and levocetirizine was excluded.

5) If possible, please include reference numbers in all figures for the meta-analysis results (Figures 2-10). I find it much easier to have reference numbers next to the authors' names (the same format as Table 1). If it is hard to change, the current version is fine.

Thank you very much for your suggestion! We have added reference numbers to all figures.

References