Reviewer’s report

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

Version: 1 Date: 29 Mar 2019

Reviewer: Emanuel Raschi

Reviewer's report:

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.
- 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 It is unclear if search and analysis of unpublished data were also undertaken (see paragraph "search strategy", last sentence).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.
- 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 alla 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)
- 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.

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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Please indicate the quality of language in the manuscript:

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