Author's response to reviews

Title: Effectiveness of psychotherapeutic, pharmacological, and combined treatments for chronic depression: a systematic review (METACHRON)

Authors:

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Author's response to reviews: see over
Dear Editor,

thank you for reviewing the manuscript and giving us the opportunity to revise it. We are also grateful for the helpful comments of Dr. Furukawa, which we were glad to address in the revised manuscript.

Please find a point-by-point response to the received comments below.

1. EDITORIAL REQUESTS

   1.1. Authors' contributions - Please format the Authors' contributions as follows: For the Authors' contributions we suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

      We have revised the Authors' contributions accordingly.

2. PEER-REVIEWER: MAJOR COMPULSORY REVISIONS

   2.1. The authors list many interventions and comparisons but have not been explicit which comparisons they are going to make. More specifically I wonder if the authors want to
make very broad comparisons by pooling "psychotherapies" "pharmacotherapies" and "combined treatments", or if they intend to make more specific comparisons. Although likely to be very heterogeneous, I think the study hypotheses require that the authors make the 3 overall compaisons (psychotherapies vs pharmacotherapies, pharmacotherapies vs combinations etc) first, and if they do turn out to be heterogeneous then look for sources of heterogeneity.

Thank you very much for highlighting this important point. We have added a subsection “Planned treatment comparisons” to the “Data synthesis” section of the revised manuscript. During the project development we discussed this issue with the head of the Cochrane Depression, Anxiety and Neurosis Group, Dr. Rachel Churchill. According to the recently changed policy of the Cochrane Collaboration she recommended a rather “bottom-up” approach, i.e. first analyzing more specific treatments and then pooling results in a multiple treatments or so called umbrella review. As we plan to provide recommendations for clinical practice on the substance (pharmacotherapy) and method (psychotherapy) level, we judge these specific comparisons to be inevitable. However, we also agree with Dr. Furukawa, that more global comparisons may provide important information. We believe, that both specific and global analyses are necessary and the question is rather: which approach should we declare as primary and which one as secondary? We believe that the study will produce a large amount of findings. Therefore, also due to dissemination reasons in form of scientific publications, we have decided to find a compromise between the global and the specific approach. We have grouped both the psychotherapeutic and pharmacological treatments according to consensual classifications (as for example in the Depression in Adults guideline from NICE and also in the Cochrane Collaboration) and will review primarily on this level. After these “meso-level” analyses we perform both the more global and the more specific data synthesis.

2.2. The authors state that they intend to abide by the ITT principle. Very typically a study gives the number of patients (1) who drop out early and never return, (2) who drop out after one or two visits and whose scores are LOCFed, and (3) who complete the study. It will help both the authors and the readers if the authors can state how they intend to deal with all of these people.

We have provided more detailed information on our approach in the “Data synthesis” section (subsection “Meta-analysis”) of the revised manuscript. For the primary
efficacy outcome (response), people dropping-out any time will be classified as non-responder, irrespective of the point of attrition (option (1) above). For secondary outcomes (mostly metric) the approach of the authors of the primary studies will be used (in most cases modified intent-to-treat analysis with LOCF; option (2) above). We consider option (3) as per-protocol data and will not mix it with ITT data, but use them in sensitivity analyses instead (see subsection “Sensitivity analysis”).

3. PEER-REVIEWER: MINOR ESSENTIAL COMMENTS

3.1. The English will benefit from some brush-up here and there.

We have made use of copyediting by a native-speaking colleague in order to improve the English of the revised manuscript.

Please do not hesitate to contact me if you have any questions.

We are looking forward to your response.

With kindest regards,

Levente Kriston
(on behalf of all authors)