PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Citalopram for major depressive disorder in adults: a systematic review and meta-analysis of published placebo-controlled trials**
AUTHORS	Apler, Alex

VERSION 1 - REVIEW

REVIEWER	***José Luis R Martin*** Head of Clinical Research Department FISCAM-Toledo Spain
REVIEW RETURNED	14-Mar-2011

GENERAL COMMENTS	Dear author, This is a well conducted systematic review of citalopram for the treatment of MDD. I would like to discuss some points: 1. Why published studies? Everyone knows that negative results are found most of the time in grey literature. Even more, what about ongoing trials? 2. The meta-analysis were in favor of citalopram so, did you search for a possible publication bias? 3. No one help you about any doubt for trial methodology, quality, inclusion criteria, etc.. How did you resolve these questions? 4. You should explain properly what change from baseline means: For example, how many different scales and versions were in the meta-analysis. 5. Remission: there are two studies included in the review with available data for this outcome but you did not do a meta-analysis. I could guess that the pooled results of these two trials will be in favor of citalopram. Why you did not make a meta-analysis of this outcome? 6. What means “significantly better statistically, but not clinically….” For this conclusion, did you use a NNT or similar? Do you know exactly what means a standardized measure like -0.27 points? 7. I think you can show (analyze) others overall effects (statistically) than just change from baseline.

REVIEWER	***Andrea Cipriani*** University of Verona Department of Medicine and Public Health
REVIEW RETURNED	14-May-2011

GENERAL COMMENTS	The present manuscript is limited to published data and this may seriously affect results and my main concern is about the inclusion of only published material in the present manuscript. The issue

	about unpublished data in psychopharmacology is a hot issue, because it is known that unpublished data may affect treatment estimate (Turner et al., 2008 - NEJM). I can see that quality of unpublished data may be difficult to be assessed (because unpublished material doesn't follow the usual peer-review process), however it is well recognised that the exclusion of unpublished data in the field of antidepressant trials may change results (Eyding et al, 2010 - BMJ). There are also some methodological issues: - a systematic review should be carried out by at least two reviewers to check study selection and data extraction (see Cochrane Handbook - www.cochrane-handbook.org) - please, use the most recently updated version of the quoted references for NICE guidelines (2010) and Cochrane Handbook (2011) - I suggest to use PRISMA statement and no more CONSORT (see ref. 21 of the manuscript) - more details about the analysis of at least primary outcome should be added - the results section and tables tend to duplicate the same information. The manuscript text could be shortened - in the results section data about remission used different cut-off criteria than those specified in the methods of the review. Please clarify - the discussion should focus on results from the present study and not to discuss general questions about antidepressants - in the discussion the first sentence seems to me to me a wrong assumption or a wrong interpretation of data. Please clarify - I suggest to follow the Cochrane Handbook more properly (even for the risk of bias issue) - A suggestion: table 5 somehow duplicates the forest plot (might be worthwhile to delete the table) Andrea Cipriani, M.D. Ph.D. WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation Department of Public Health and Community Medicine, Section of Psychiatry and Clinical Psychology, University of Verona, Policlinico "G.B. Rossi", Piazzale L.A. Scuro 10, 37134 Verona, Italy.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: José Luis R Martin
CastileLa Mancha Health Research Foundation, Clinical Research

Dear author,

This is a well conducted systematic review of citalopram for the treatment of MDD.
I would like to discuss some points:

1. Why published studies? Everyone knows that negative results are found most of the time in grey literature. Even more, what about ongoing trials?

Please see my response to point 8, below. Exclusion of unpublished studies was mentioned as a limitation in my review.

2. The meta-analysis were in favor of citalopram so, did you search for a possible publication bias?

I examined small study effects via assessment of asymmetry in the funnel plot. Publication bias is one potential source of plot asymmetry. I did not have access to unpublished studies to carry out a more detailed assessment of publication bias.

3. No one help you about any doubt for trial methodology, quality, inclusion criteria, etc.. How did you resolve these questions?

The following statement was included in the methods section: I reviewed each paper on at least two occasions, to check for accuracy of selection and data extraction, over a three month period.

The following paragraph was added to the discussion section: This review has been undertaken by a single reviewer. While a single reviewer may be able to select and extract unambiguous data, additional reviewers can help reach consensus regarding areas of ambiguity in published reports. That consensus, however, should not replace missing or ambiguous data, or substitute the importance of adequate reporting that is necessary for a systematic review.

4. You should explain properly what change from baseline means: For example, how many different scales and versions were in the meta-analysis.

I inserted the following sentence into the Secondary Outcome section in Methods: Any reduction in the severity of depression, measured as a reduction in scores relative to baseline values (change from baseline), on the HAM-D, MADRS or CGI scales.

I inserted the following phrase into the meta-analysis section in Methods: “on the 17, 21 and 24-item HAM-D scales”

5. Remission: there are two studies included in the review with available data for this outcome but you did not do a meta-analysis. I could guess that the pooled results of these two trials will be in favor of citalopram. Why you did not make a meta-analysis of this outcome?

Please see my response to point 12 below.

6. What means “significantly better statistically, but not clinically….” For this conclusion, did you use a NNT or similar? Do you know exactly what means a standardized measure like -0.27 points?

I removed the reference to the effect size of 0.5 or higher being clinically significant: this is a concept that was used in the previous NICE Depression Guideline (CG23), but not in the current one (CG90).

I explained in the Results section that standardized mean difference (SMD) of -0.27 indicates that the improvement in the HAM-D scores of subjects treated with citalopram was 0.27 standard deviations better than the improvement in those treated with placebo.

7. I think you can show (analyze) others overall effects (statistically) than just change from baseline.

I added a meta-analysis of the response rates, but could not perform a meta-analysis of the remission rates for reasons given at point 12 below.

Reviewer: Andrea Cipriani, M.D. Ph.D.
WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation
Department of Public Health and Community Medicine,
Section of Psychiatry and Clinical Psychology,
University of Verona, Policlinico "G.B. Rossi",
Piazzale L.A. Scuro 10, 37134 Verona, Italy.

8. The present manuscript is limited to published data and this may seriously affect results and my main concern is about the inclusion of only published material in the present manuscript.

The issue about unpublished data in psychopharmacology is a hot issue, because it is known that unpublished data may affect treatment estimate (Turner et al., 2008 - NEJM). I can see that quality of unpublished data may be difficult to be assessed (because unpublished material doesn't follow the usual peer-review process), however it is well recognised that the exclusion of unpublished data in the field of antidepressant trials may change results (Eyding et al, 2010 - BMJ).

I included the following paragraph in my discussion: This systematic review is limited to published studies. Its results are subject to a review of unpublished research and outcome data that is missing from published reports. Nevertheless, this review may serve as a useful summary of published data, highlighting the risk of bias and the paucity of published research into the effect of citalopram on remission of MDD.

9. A systematic review should be carried out by at least two reviewers to check study selection and data extraction (see Cochrane Handbook - www.cochrane-handbook.org)

Please see my response to point 3 above.

10. Please, use the most recently updated version of the quoted references for NICE guidelines (2010) and Cochrane Handbook (2011)

I updated my references to the most recent guidelines.

11. I suggest to use PRISMA statement and no more CONSORT (see ref. 21 of the manuscript)

I carried out the meta-analysis in accordance with the PRISMA statement, and submitted the PRISMA checklist with my review. I removed the reference to the CONSORT statement.

12. More details about the analysis of at least primary outcome should be added

I calculated the relative risk and 95% confidence intervals for the remission rate in the paper by Stahl. I could not perform a further analysis on the paper by Lepola, given the missing remission rate for the placebo group, and therefore I could not perform a meta-analysis of these two studies.

13. The results section and tables tend to duplicate the same information. The manuscript text could be shortened

I removed the tables, to make way for an additional meta-analysis and the funnel plot.

14. In the results section data about remission used different cut-off criteria than those specified in the methods of the review. Please clarify

Remission was defined in Methods as a score of 7 or less on HAMD-17 or a score of 11 or less on

MADRS. This is consistent with the definition of remission used by Stahl (score of less than 8 on HAMD-17), and with that used by Lepola (score of less than 12 on MADRS). I modified the wording in the Methods section to make this clearer.

15. The discussion should focus on results from the present study and not to discuss general questions about antidepressants

I shortened and revised the Discussion section.

16. In the discussion the first sentence seems to me to me a wrong assumption or a wrong interpretation of data. Please clarify

The Discussion section was revised.

17. I suggest to follow the Cochrane Handbook more properly (even for the risk of bias issue)

I updated the assessment of bias, to be consistent with the current Cochrane Handbook, version 5.1.0.

18. A suggestion: table 5 somehow duplicates the forest plot (might be worthwhile to delete the table)

Table 5 was deleted

VERSION 2 - REVIEW

REVIEWER	***José Luis R Martin***
REVIEW RETURNED	06-Jul-2011

RESULTS & CONCLUSIONS	Dear Editor The results of this manuscript are limited by these two points (therefore increasing the risk of bias): 1. The author uses only published studies (risk of publication bias) 2. There is only one author (therefore there is not discussion about different points of view: clinicians vs researchers, for example). This normally improve the quality of any review. On the other hand, these limitations are explained in the text. So, it is difficult to choose an appropriate recommendation for its publication or not. In my point of view this manuscript could be published but clearly highlighted these two important points.