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.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently reviewed again at BMJ Open and accepted for publication.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review
AUTHORS	Lucy E Farrimond, Emmert Roberts and Rupert McShane

VERSION 1 - REVIEW

REVIEWER	Claudine Berr INSERM
REVIEW RETURNED	03/10/2011

GENERAL COMMENTS	This paper presents results of a systematic review, meta-analysis, and sensitivity analyses to examine the impact of these issues and of the inclusion of unpublished data on the efficacy of combination memantine and AChEI therapy in moderate-to-severe AD. First, major interest of this paper is that it raises the problem of unpublished trials and illustrates how decisions of inclusion/exclusion in review or meta analysis are made. One of the major lessons is that results can changed easily depending largely on the methodological choices. The introduction well explained how choice, selection of data for expertise, review or Meta-analyse can change or influence practice and guidelines. Few or slight changes can really influence results and subsequent decisions at different levels This is well known by many scientists but it is important to illustrate. Generally it is suggested that publication bias lead to underestimate negative results. In this analysis, inclusion of non published data increased power of analyses and allow to show , on the same level, results with 4 outcomes (clinical global, cognition , function and behavior /mood). The discussion on unpublished data is really important Second, results are important for clinicians, in a context where estimated medical service and reimbursement of these drugs are discussed again by the governmental agencies (in France, particularly) The estimate after a meta-analysis is closer to the effect likely to be obtained with the practical use in "real life". Some points should be clarified or modified in order to improve this interesting paper - Page 3 line 15: Be clearer and/or sharper on the message to get across to the conclusions that can be derived from a non systematic review. This term should be defined - In results, is it possible to better describe the clinical magnitude of the statistical significant improvement of trials included in this review. Mean differences are presented in figure 1 but they are not illustrative for readers who do not know the scales which are specific of AD trials - In the discussion,

	- the importance of declaration on conflict of interest should be emphasized - The inclusion of conference posters is questionable as they are not available easily and their quality is difficult to evaluate. Conference posters give only some indices on advancement of trials

VERSION 1 – AUTHOR RESPONSE

Itemized Responses to BMJ Committee and Reviewer Comments

Report from the BMJ's manuscript meeting (including the Reviewer's comments)

"This paper ... should have incorporated much more methodological detail than is currently the case. More specifically:

1. ***There is no assessment of quality of included studies***

This is now included in the Results section.

2. ***The search strategy is not given in full here, and also you don't seem to have searched Medline***

The full search strategy is now described in the Methods section. It includes Medline.

3. ***Data extraction procedure is not detailed, and we don't know if anything was double-checked***

The data were extracted independently by at least two people and discrepancies were resolved by discussion.

4. ***There is no description on the choice of meta-analysis method (the paper simply says you used Revman). The figures reveal a random-effects meta-analysis was used, but this needs explanation in the methods.***

A random effects meta-analysis was used. This is now explained in the methods.

5. ***The meta-analyses (mainly) pool standardised mean differences, and it is very hard to understand what the estimates mean clinically. For example, in the abstract you say there is a 'small benefit of combination therapy' – what is this benefit clinically? We can't tell on the scale provided. Why have the original scale scores not been used?#***

Presenting treatment differences as standardised mean differences (SMDs) (the absolute mean difference divided by the standard deviation) enabled us to pool data when different original scales were used by the included RCTs. In the TA217 assessment report, all effect sizes were presented as weighted mean differences (WMD), and data was not pooled when included trials used different rating scales. Although it is possible to it is possible to 'back translate' the overall standardised effect size to an approximate equivalent score on a scale, too many assumptions are made in doing this.

The point about the clinical relevance of the effect size is a good one. The debate over what constitutes a clinically meaningful difference is rehearsed elsewhere (e.g. Howard et al Int J Geriatr Psychiatry. 2011 Aug;26(8):812-7; Molnar et al Am Geriatr Soc. 2009 Mar;57(3):536-46). We have added sentences prominently in the Discussion and the abstract's Conclusion to make the point that the clinical relevance of the findings is not robust since whether the clinical global is significant depends on exactly which trials are included.

6. ***In a single trial, the crucial thing when looking at mean differences is that the groups were balanced at baseline in the score of interest. We have no idea if that was true in each of these trials. And what methods in each trial were used to estimate the mean difference between groups (did you adjust for baseline for example?). Different analysis methods may well be causing differences across trials in the standardised mean differences we are observing here .***

The baseline characteristics of participants in included trials are now given in Table 1. The primary studies included were adjusted at baseline. The values in each trial were the means of the differences between baseline and endpoint scores. This is a standard technique used in dementia trials and is the same across all trials.

7. ***In Table 1 you do three analyses per outcome, depending on the data included. But how can we compare the three analyses when one uses a weighted mean difference as the effect measure, and the others use a standardised mean difference. Differences may simply be due to the use of different effect measures.***

For comparison, we have replicated the findings of the TA217 report, presenting them first as WMDs (as in the original report) in Analysis 1a, and then as SMDs in Analysis 1b for comparison with the results of our sensitivity analyses (Analyses 2 and 4) (see Table 2). In the TA217 assessment report, all effect sizes were presented as weighted mean differences (WMD), and data was not pooled when included trials used different rating scales. In this review, we presented effect sizes as standardised mean differences (SMDs). This is a legitimate technique which is routinely used in meta-analysis (See Cochrane Handbook Chapter 9. (See point 5, above).

8. ***Currently, the abstract does not make it clear how the conclusions are arrived at"***

The abstract now describes the results as per the sensitivity analyses.

Reviewer Comments

1. ***"Page 3 line 15: be clearer and/or sharper on the message to get across to the conclusions that can be described from a non-systematic review – this term should be defined***

This has been noted and the sentence amended accordingly.

2. ***In results, is it possible to better describe the clinical magnitude of the statistical significant improvement of trials included in this review. Mean differences are presented in figure 1 but they are not illustrative for readers who do not know the scales which are specific of AD trials***

See point 5 in the responses to the report from the BMJ's manuscript meeting.

In the discussion:

3. ***the importance of declaration on conflict of interest should be emphasized***

This is noted and has been amended.

4. ***The inclusion of conference posters is questionable as they are not available easily and their quality is difficult to evaluate. Conference posters give only some indices on advancement of trials"***

This is noted, although we do not include data from posters. However, we actually think posters are important because they sometimes are the only place in which important clinical data are presented. In our view, the risks of publication bias are greater than the risks that the data will change significantly in the process leading to ultimate publication. This is particularly true in cases where there are long delays in publication.

VERSION 2 – REVIEW

REVIEWER	Dr Mark Simmonds Research Fellow Centre for Reviews and Dissemination University of York UK I have no competing interests.
REVIEW RETURNED	01/03/2012

THE STUDY	1. Given the stated aims, included trials should compare memantine + AChEIs vs AChEIs alone. The "Trial Inclusion Criteria" section, however describes apparently different inclusion criteria and the forest plots give the impression that these are trials of memantine vs placebo. I think this is a lack of text clarity rather than an error in inclusion criteria, so the relevant sections should be rewritten and forest plots amended. 2. What meta-analysis methods are used? I assume DerSimonian-Laird random effects? Please clarify.
RESULTS & CONCLUSIONS	3. (Results of synthesis) This section is rather short and unclear. I think it should be expanded to make clearer the differences between your analyses and the TA217 analysis and to explain the results in the forest plots and table 2 in more detail. Specific reference should be made to the forest plots.
GENERAL COMMENTS	Some minor points which require clarification: 4 Make it explicit that donepezil is an AChEI. 5. (Data extraction) You state that where data were not available from primary reports data were taken from a previous meta-analysis. How did this meta-analysis obtain the data? Is it reliable? Please comment. 6. (Data synthesis) "four clinical domains were pooled". I assume you mean pooled separately and independently? Please clarify. 7. (Description of studies) I found this section difficult to follow. I suggest re-writing to make absolutely clear which studies were included and why, and which excluded and why. 8. (Outcome measures) A table showing which measurement scale belongs to which clinical domain, and which scale was reported in which trial would be very helpful here. 9. Has the Cochrane Review of which this analysis forms a part been published? If so provide a reference.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Dr Mark Simmonds
Research Fellow
Centre for Reviews and Dissemination

University of York
UK

1. Given the stated aims, included trials should compare memantine + AChEIs vs AChEIs alone. The "Trial Inclusion Criteria" section, however describes apparently different inclusion criteria and the forest plots give the impression that these are trials of memantine vs placebo. I think this is a lack of text clarity rather than an error in inclusion criteria, so the relevant sections should be rewritten and forest plots amended.

The relevant section has been re-written to clarify this point. The Forest plot axes are relabelled as 'Memantine + ChEI' and 'ChEI montherapy'.

2. What meta-analysis methods are used? I assume DerSimonian-Laird random effects? Please clarify

Yes. This has been clarified in the revised draft.

3. (Results of synthesis) This section is rather short and unclear. I think it should be expanded to make clearer the differences between your analyses and the TA217 analysis and to explain the results in the forest plots and table 2 in more detail. Specific reference should be made to the forest plots.

We agree and have re-written, signposting the Analyses in the Table.

Some minor points which require clarification:

4. Make it explicit that donepezil is an AChEI.

This has been amended.

5. (Data extraction) You state that where data were not available from primary reports data were taken from a previous meta-analysis. How did this meta-analysis obtain the data? Is it reliable? Please comment.

The meta-analysis was a company sponsored meta-analysis and had direct access to the primary data.

6. (Data synthesis) "four clinical domains were pooled". I assume you mean pooled separately and independently? Please clarify.

Data from the four domains were pooled separately and independently, this point has been clarified in the text.

7. (Description of studies) I found this section difficult to follow. I suggest re-writing to make absolutely clear which studies were included and why, and which excluded and why.

The relevant section has been rewritten to clarify these points.

8. (Outcome measures) A table showing which measurement scale belongs to which clinical domain, and which scale was reported in which trial would be very helpful here.

We have removed this from the text and put it into the table for clarity.

9. Has the Cochrane Review of which this analysis forms a part been published? If so provide a reference.

Please see comments above.