Article details: 2015-0057	
Title	Treatment for Mild Cognitive Impairment: Systematic Review and Meta-analysis
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Reviewer 1	MM Leeflang
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General comments (author response in bold)	R1.general. This manuscript describes a systematic review about treatments for mild cognitive impairment. Overall, the number of outcomes and the number of interventions make this manuscript a difficult one to read and to keep track of. I understand that the alternative (splitting the review into different treatments) poses again other problems. **We have added results for test for sub-group differences based intervention type. Various treatment options were grouped based on type and this approach is consistent with previously published reviews on cognitive impairment.** R1.1 General remark: My first question is how this review relates to already published work in the Cochrane Library. None of the authors in this project seems to have been involved in any of the Cochrane reviews on the same topic. For example, the review by Russ and Morling (Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD009132. DOI: 10.1002/14651858.CD009132.pub2.) contains largely the same studies as the submitted manuscript (for the cholinesterase inhibitors). Their conclusion is also quite similar. None of the Cochrane reviews has been referenced in this manuscript, while I think they should be. **In our interpretation section we have added references Russ and Morling review and noted that the findings of our review were consistent with the findings of their earlier review. We also looked at the Cochrane reviews by Martin et al (2011) and Farina et al (2012) however both of those reviews reported on outcomes which were not of interest in our review.** R1.2 The authors did a very extensive search, no comments on that. The only thing is, as they mention themselves as well in the Interpretation section, that the search may be outdated (done in 2012). Why not update it? **Our search in the submitted manuscript was an update of the 2012 search by Lin et al. that update was to Dec 2014. However during this revision period we have conducted another update (August 2015).** R1.3 Page 4. Were Risk of Bias assessment also done by two researchers independently? Were the data abstraction forms piloted first? Not sure if I understand the statement "independently verified all the extracted data" (page 4, lines 21-22). I think data extraction is either done independently, or data provided by one person are checked by another person (but then it is no longer independent from each other, because the second person knows what the first person scored). **We have added additional details on risk of bias and re-worded our statements on verification processes.** R1.4 Why did the authors choose to express their results as mean differences and not as relative risks? Would it be possible to provide a brief explanation of what the mean differences mean? On page 4, the authors do explain that it is calculated using change from baseline data; but it is not explicitly stated that they probably mean that the MD is the difference in change from baseline data between the two treatments. On page 8, lines 12-13 they state that there was a small benefit of pharmacological treatments of "1.01 higher MMSE score (CI 0.25 to 1.77 higher)", but it is not the actual MMSE score that is reflected by the MD (as explained in the methods section). Or did I get this completely wrong? **Relative risk was not used as a summary statistic because studies did not dichotomize the outcome data based on MMSE and ADAS-cog scale. The MD as summary statistic is**

	difference in change from baseline to immediate post-treatment between two treatment arms or in other words difference in improvement on a continuous scale. The sentence has been rephrased for more clear interpretation. R1.5 Is it necessary to use so many digits for the MDs and RRs? I would think two or three are more than sufficient. **Since summary statistic is actually a difference in change or improvement, therefore more decimal places allows the proper inclusion of very small effect observed**. R1.6 The authors do not report whether the decision to pool or not was based on the reported Cochran's Q or I-square. I suppose it wasn't, but it would be nice of that was explicitly mentioned. **Statistical heterogeneity was considered as a part of overall quality assessment using GRADE and studies were pooled and sub-grouped based on homogeneity in type of intervention and outcome measure used.** R1.7 Meta-analyses and forest plots. The authors seem to have done a meta-analysis even if there were only one or two studies. I think this is redundant and unnecessary. And please refer to the appropriate forest plot / figure in the appropriate places, rather than just referring to all forest plots at once. For a reader it is now impossible to see directly which forest plots relate to which analyses (see next point in particular). **An estimate of effect was provided or calculated for single study outcomes in the form of Mean difference (MD) for consistency with other outcomes, as included study may not have reported the outcome using same parameters or units. Forest plots were used for visual display as effect estimates may not be available directly from study. Also for each effect estimate we have added the reference to specific figure it relates to.** R1.8 Figure 7, about the non-pharmacological interventions. From the figure it is not clear how many different non-pharmacological treatments were analyzed here. Not how different these treatment s are from each other and thus whether they really could have been put together or not. Please provide some more explanation to this figure. **We have added the type of non-pharmacological interventions in results section. They are discussed in "indirectness" domain of GRADE tables (footnote 45) and also described in characteristics of studies table. Due to text size and space constraints in a forest plot, the information could not be added directly to the figures.** R1. 9 Adverse events: please explain how adverse events were handled. Were they all taken together? Or did the authors focus on two or three subgroups of adverse events? Please explain what the risk ratios mean. What I am specifically surprised by, is that the control groups have quite some adverse events as well. Especially as they seem to receive a placebo. Not sure if it relevant for this review and this audience, but I would have liked some more information about the adverse events. **Description of adverse events added to narrative. Both hospitalization and death were considered as serious adverse events. Risk ratio provides the relative risk of having a serious adverse event in treatment group as compared to control.** R1.10 GRADE Tables. I understand the value of these tables and their footnotes. But the footnotes really make the table difficult to read and to interpret. Would there be a way to work around this and to limit the number of footnotes as much as possible? **Each body of evidence is quality assessed separately in GRADE and we did try to minimize the number of footnotes regarding each judgment by cross referencing if they were similar across outcomes, however if they were different in terms of reasoning , they need to be presented separately.** R1.11 Page 8, lines 21-22: "Our review fills a research void in the treatment of MCI.". I am not sure whether I can agree with this statement. See comment 1, about the existing Cochrane reviews. At the moment, there seem to be more reviews on this topic than

	primary studies… **We have changed this statement to…" To our knowledge this review is the first review which consolidates treatments while focusing specifically on people with a diagnosis of MCI.** R1.12 It would have been helpful if the authors would have checked the PRISMA statement and if they would have provided the checklist with the manuscript. But I think (after a quick check) they have fulfilled all the items. **PRISMA checklist has been completed.**
Reviewer 2	Nishant Mishra
Institution	Department of Medicine, University of Glasgow, Glasgow, Scotland
General comments (author response in bold)	R2.1 This is a well written article. The authors systematically evaluated the published data on the efficacy, safety, and adverse events after the use of therapeutic and behavioral interventions in patients diagnosed with mild cognitive impairment. It is obvious from this systematic review that investigators of the individual studies studied in this review used different therapeutic or behavioral interventions, applied disparate methodologies to examine outcomes in dissimilar patient populations (e.g. some enrolled patients with MCI vs. only amnestic MCI), used a variety of outcome measures (ADAS-COG, MMSE, etc.), assessed outcomes at slightly different time points, and so on. Further, in certain subgroups, fewer studies were available: in figure 4, only one study is meta-analyzed, and in figure 3, only one rivastigmine study is included. While the authors have reported statistical heterogeneity, authors haven't highlighted the sources of clinical heterogeneity. I wonder if the patients receiving different interventions (a variety of drugs, behavioral interventions, etc) can be pooled together in a meta-analysis. Authors may want to highlight this problem and make recommendations about the common data points and outcome measures that should be used in the future trials to allow comparability. Study categorization in to different intervention groups was considered based on type of drug used and also evidence from existing reviews (USPSTF). We do recognize the limitation of this approach as there may be differences within each intervention category such as behavioral interventions, but such differences are mentioned and assessed in directness domain of GRADE and evidence was graded considering both statistical heterogeneity in inconsistency domain and clinical heterogeneity in indirectness domain. **We have added a statement in the section on Conclusions and implications for practice and future research** R2.2 Authors should identify and clearly report the primary endpoints (outcome measures) used in the individual trials; outcome using these measures should be analyzed separately and reported under one sub heading, i.e., primary endpoints. Then the outcome analysis using secondary endpoints can be reported. **The primary and secondary end points for each study are provided in characteristics of included studies table. We only considered the outcomes and validated outcomes measures reported by TRICCO et.al.** R2.3 Authors do not list adverse events. In the flow diagram 1, the authors should report what were the "other sources". In figure 4, only one study is meta-analyzed, and in figure 3, only one rivastigmine study is included. **Serious adverse events have been listed (hospitalization or death)** **Flow diagram has been altered to read: Additional records identified through high quality systematic reviews**
Reviewer 3	Theodore Cosco
Institution	MRC Unit for Lifelong Health and Ageing at UCL, London , UK
General comments (author response in bold)	R3.general The authors conduct a systematic review and meta-analysis of treatments for mild cognitive impairment (MCI). They have conducted a comprehensive review and have captured some interesting studies on MCI treatment and outcomes, addressing the

	limitations and reporting these results appropriately. I do, however, have some concerns about the conceptual framework surrounding MCI and the dearth of studies available for meta-analyses. R3.1 As acknowledged by the authors, MCI is a contentious topic (Tang, Brayne et al. 2015). I worry that with the diversity of definitions for MCI like may not be compared with like; different definitions may result in different outcomes e.g. (Ganguli, Snitz et al. 2011). Further articulation of the ways in which MCI is operationally defined and/or which subtypes are being examined in the studies is necessary to address these issues. **We have added a paragraph in the introduction of the manuscript which highlights the contentious nature of the operational definition of MCI.** R3.2 Meta analyses are often difficult in being able to compare like with like. In line with my previous comment, it is imperative that these meta-analyses are being conducted in studies that are comparing the same MCI subtypes or using the same operational definitions of MCI. If possible, the meta analytic studies should be using the same MCI conceptualisations. **The operationalization of MCI definitions and sub-types are challenging and contentious as discussed in literature (Golomb et al.) Not all of included clearly described the type of MCI diagnosed, so to maximize the number of included studies we considered MCI (however defined). This has been acknowledged as a limitation.** R3.3 A PRISMA statement is not included **A statement that we have adhered to PRISMA has been added.** *Reviewer #3 Minor Comments* R3M1. Inconsistent referencing system, i.e. numbered in some places and APA in others, e.g. pg 3 line 17 & 21. **Referencing system has been reformatted** R3M2. Appendix A is unclear as to what search strategy was used for this investigation. Was the MCI review picked from a broader review? **In the narrative section of the manuscript we have added additional detail about how the search was developed and, more specifically, that we used a comprehensive search strategy developed by Lin et al and narrowed it with specific search terms for MCI.** R3M3. Ganguli, M., B. E. Snitz, et al. (2011). "Outcomes of mild cognitive impairment by definition: a population study." Arch Neurol 68(6): 761-767. Tang, E. Y., C. Brayne, et al. (2015). "Mild cognitive impairment definitions: more evolution than revolution." Neurodegener Dis Manag 5(1): 11-17. **Thank you for these references. We have looked at these papers and incorporated these as references in our introductory section.**