Reviewer's report

Title: Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis

Version: 3  Date: 15 November 2014

Reviewer: Jesse Berlin

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Major Compulsory Revisions:

1. I very much appreciate the transparency, but why not register the protocol with PROSPERO? (This isn’t so much a revision to the paper as a revision to the strategy.

2. Page 8 of 13: You calculate the SMD for each paper. Is that based on the final value of the scale compared between treatment arms? Is that always reported? What about if you find only a result based on covariate adjustment for baseline differences? What if the study only reports change from baseline? These are subtleties but they are important subtleties, as reporting on them would affect the trained reader’s ability to reproduce your findings, given the data. (I’m far from an expert on SMD calculation, so can’t really help with specifics on how to deal with various combinations of adjustment for baseline values, limiting to final values, and using change from baseline.)

3. Page 8 of 13: What dichotomous variables are you referring to (as outcome variables)? You mention remission separately, so is this about adverse events? Please clarify.

4. Using pooled experimental groups assumes the various interventions have similar effects to each other. Can you examine the validity of that assumption? You risk diluting the effect of more potent interventions, don’t you? For example, is you have a study with different “doses” of exercise, wouldn’t the lower dose groups dilute the effect (potentially) of the higher dose groups? There are other statistical approaches to this, including mixed treatment comparisons / network meta-analysis.

5. What random effects model to you plan to use? Is it DerSimonian-Laird (because it’s the default in RevMan?) I won’t get into the debate over the fact that this method is not ideal, but you should at least be explicit about what approach you’re planning to use.

6. Several studies have been published since the earlier analysis you did in 2010. I’m really not at all sure why that leads to needing to do (or the perceived need to do) a sequential analysis. Is your idea mainly to define the time point at which the overall result becomes statistically significant (if it does become significant)? Why is that important to know in the context of the current analysis?
Is the idea to define the need for further studies, when you’re done, assuming the summary result is not conclusive (i.e., you would be defining a future research program)? My sense is that the method is generally aimed at correcting for repeated analyses over time, but that’s not what you’re doing. You are picking a single point in time (now) and doing a single meta-analysis. (Admittedly, there was one prior “look” at the data, in 2010, so some tempering of a conclusion of benefit might be required). In any event, you could use a clear rationale for the approach.

Minor Essential Revisions:
7. I’m not making specific suggestions, but the writing could benefit from some close editing.

8. While sensitivity analysis is always a good thing, I’m guessing that the value of the sensitivity analyses will depend on the extent of missing data. Some of the results may be obvious when there are extensive missing data, especially if the missing-ness is not equally distributed between groups. For example, if 60% (it’s an extreme example, I admit) of subjects discontinue in the exercise group, compared with only 30% in the control groups, you’d be adding a lot of failures to the exercise group, relative to the control group, and I think the result will be obvious.

One might view “discontinuation” from the study as a sign of lack of effectiveness of the intervention, or that the intervention is poorly “tolerated.” (I got tired of exercising and it wasn’t helping anyway.) I suppose someone could also discontinue if he/she is feeling very much better. Do you have any prior data on reasons for dropout that might help guide these analyses? Can you extract reasons for dropout from the studies?

Discretionary Revisions
9. I’m suggesting this in the interest of adding an exploratory methodological aspect to the paper. I understand the value in looking specifically at clinical depression. Would there be value in contrasting results with the same analysis done by this same group) looking at patients classified as depressed on the basis of psychometric testing? (Some form of meta-regression or stratified analysis could be done). This kind of approach seems potentially relevant given that one of the primary endpoints is score on a depression scale.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I am a full-time employee of Johnson & Johnson, but see no conflict in reviewing this paper, which focuses on the value of physical exercise in treating depression.