Reviewer's report

Title: Network meta-analysis of randomised trials of pharmacological, psychotherapeutic, exercise and collaborative care interventions for depressive symptoms in patients with coronary artery disease: hybrid systematic review of systematic reviews protocol

Version: 0 Date: 21 Nov 2018

Reviewer: Yin Wu

Reviewer's report:

The objectives of this network meta-analysis (NMA) are to "compare the best-established treatment(s) for depression in patients with coronary artery disease (CAD) in terms of efficacy (or effectiveness, in studies using non-placebo comparators) and acceptability, with several secondary outcomes also considered." The proposed primary outcomes are change in depressive symptoms (summarized with standardized mean difference (SMD)) and treatment acceptability (treatment discontinuation: % people who withdrew). Secondary outcomes include change in 6-month depression outcomes, health-related quality of life (HRQoL), mortality, cardiovascular morbidity, health services use, and adverse events. The authors propose this review as the first NMA to provide a ranking of treatments for depression in those with CAD. However, there are a number of methodological concerns about the conduct and reporting of a network meta-analysis that should be addressed. In addition, the review protocol is not reported in many places with sufficient detail or consistent with PRISMA.

Major Comments

1) The rationale for excluding cardiac rehabilitation because it is "currently undergoing investigation elsewhere" is inconsistent with the logic of conducting a NMA for depression treatments. The cited cardiac rehabilitation meta-analysis (reference 33) is not about treatments for depression. If cardiac rehabilitation is considered a depression treatment alternative to those included in the present NMA, then cardiac rehabilitation should be included. If it is not an intervention that would be used for treating depression, then it should be excluded. The authors should clarify this rationale.

2) The authors state that they will exclude RCTs of "psychological interventions that are not established psychotherapies delivered by trained therapists." How will this be codified for inclusion/exclusion?

3) Will the authors include abstracts? Will they seek data from unpublished studies (they say they will search trial registries)?
4) The authors state that they will do a review of systematic reviews to identify eligible RCTs for their NMA. Per the Cochrane Handbook (https://handbook-5-1.cochrane.org/chapter_22/22_overviews_of_reviews.htm), however, an overview of reviews is a synthesis of systematic review results. It would be reasonable for the authors to use existing systematic reviews as a starting point for a systematic review and NMA of primary RCTs. However, that would require a methodology for determining whether identified systematic reviews were done adequately (e.g., per AMSTAR) and would require a plan for updating to determine if there are more recent relevant trials. This would be important given the relatively small number of trials, for instance in drug interventions, and the possibility that a newer trial could feasibly change effect estimates.

5) Setting clear PICO elements is very important in NMA to ensure that the key assumption of transitivity is likely to hold. In this review protocol, the authors may need to narrow down the criteria for the eligible participants and included interventions and clarify under what conditions the transitivity assumption is likely to hold.

6) In the PICO statement that the authors present, participants of the review are patients with CAD and elevated depressive symptoms (clinical diagnosis of depression, or scoring above threshold on a validated scale). However, they do not specify the clinical diagnosis of depression, validated scale, and the threshold. Does any clinical diagnosis that is made by a clinician count as a valid diagnosis? Which scales are validated? Do the studies using the same validated scale apply the same threshold? Examples should be provided for clarification.

7) Another part of the PICO statement is the comparison. In this review protocol, comparison groups include placebo groups, usual care or waitlist control, attention control groups. Although the authors provide a rationale for the inclusion of several comparison groups, the proposed network plot is confusing. That is, since there are multiple comparator groups in the entire network, how will a single treatment ranking be generated?

8) Regarding the primary and secondary outcomes, the authors do not provide the rationale for the time windows they choose. For instance, why the week 8 post-intervention (between 4-16 weeks)/week 26 (between 20-30 weeks) is selected as the time point for SMD estimates as the first primary/secondary outcome of efficacy (effectiveness) - response (continuous)? In addition, why the range of 4-16 weeks is selected for the last secondary outcome, adverse events?

9) The search string is appended in this article, but it is adapted from an earlier work of Baumeister et al. The authors are encouraged to have the search strategy peer reviewed via the PRESS system.
10) In Data Extraction for Continuous outcomes, the authors mention that missing imputation with the median from the other studies within a same group will be used if there is insufficient data for calculating 95% confidence interval. They state that a sensitivity analysis will be followed. They need to provide rationale for their decision. Multiple imputation, accounting for the uncertainty of the imputed value, may be a better approach.

11) In Data Extraction for Missing RCT outcome data, the authors claim that "the missing data imputation is already part of the risk of bias assessment conducted in prior meta-analyses", however, the review they propose here actually includes both studies involved in prior meta-analyses and "RCTs which are listed as not having being included in the final published reviews". The authors need to specify how they would address the missing RCT outcome data in the newly-added studies.

12) In the statistical analysis section, it is unclear that how the multiple comparator groups issue is addressed in the main network analysis. Would comparison between different comparator groups, between placebo group and minimal treatment group, for instance, be included in the main network?

13) Do the authors have an a priori idea of how many eligible studies they will find for the different included interventions for CAD (excluding other heart disease patients)? That is, have they done preliminary work to ascertain the likelihood that they will be able to accrue enough RCT data to draw conclusions with any confidence? What can be understood from existing systematic reviews on included interventions.

14) For a key assumption of NMA, the authors make a plan to assess transitivity and list potential effect modifiers. "differences in placebo-controlled versus other comparator group studies" is one of the effect modifiers, but it is unclear that how these will be measured and how the differences will provide evidence for transitivity. In addition, does this mean only placebo-controlled groups are used as the comparison group in the main network? The authors need to clarify.

15) There are some areas where the reporting is not consistent with PRISMA-P and PRISMA extension statement for NMA requirements that need improvement (this is a protocol, items for reporting results and discussion are not applicable). Some examples are below.

a. Item #2: the authors are encouraged to register the protocol first because there are a large body of systematic reviews and meta-analysis in this area, there might be similar NMA already be registered.
b. Item #16: Meta-bias, for example selective reported within studies is mentioned on page 16, but no specific plan of assessment is provided.

16) The page numbers for reporting many of the items in the PRISMA-P and PRISMA extension statement for NMA requirements (the page numbers are different even referring back to the original word file they submitted) are not consistent with the main document text. The authors should double-check and ensure the readers can locate the page number correctly. For example:

a. Item #3b: contributions statement is on page 21, not 12.

b. Item #5a: Financial statement is on page 21 too, not 12.

c. Item #9: Information sources is on page 12-13, not 7-8.

d. Item #12: Date items are on page 12-13, not 8-9.

e. Item #14: Risk of bias assessment is on page 15-16, not 8-9.

f. PRISMA NMA Item #S1: Geometry of the network is reported on page 16-17 not 10-11.

g. PRISMA NMA Item #13: Summary measures is mentioned on page 19, not 11.

17) In the statistical analysis section, the authors describe the commands they will use to perform the NMA. In addition to this information, the authors should describe the statistical models that underlie these commands, and their assumptions.

18) In the statistical analysis section, the authors describe pairwise meta-analyses. Please provide a clearer rationale for these analyses.

Minor Comments

19) The authors do not check any item in the column of "Information reported" in the checklist of PRISMA-P and PRISMA extension statement for NMA requirements.
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Yes: Dr. Brett Thombs, McGill University