Combining pharmacological and non-pharmacological interventions in network meta-analysis in psychiatry

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Introduction

Network meta-analyses (NMAs) assess the comparative effects of two or more interventions, even if they have not been compared head-to-head in a trial.[1] The validity of NMAs is founded on the assumption of *transitivity*, i.e., that effects modifiers do not significantly differ across the included trials.[1] The popularity of NMAs on pharmacological *or* non-pharmacological interventions is increasing in psychiatry.[2] Recent NMAs have even combined pharmacological *and* non-pharmacologic interventions in the same network. Although this may be highly informative for guidelines development, it is methodologically challenging, and could compromise the validity of NMAs. We thus set out to evaluate NMAs that combined pharmacological and non-pharmacological interventions and provide some guidance on how to conduct them.

Methods

We searched Pubmed, PsycInfo, Embase, OVID Medline, Biological abstracts, Biosis and Web of Science until 31.08.2018. We appraised NMAs of RCTs based on the approach proposed by Cope et al.,[3] focusing on: a) how the *control node* (or neutral comparator) was defined in the network geometry; b) differences between pharmacological and non-pharmacological studies with respect to patient characteristics; c) distribution of risk of bias (RoB) in the network. According to the Cope's approach, we checked if the impact of these issues on results was explored in the retained NMAs (See eMethods for more details).

Results

We retrieved 12 unique NMAs (See eReferences). Eight were published between 2017 and 2018; 6 focused on adults, 5 on children/adolescents, and one on both. These NMAs covered several psychiatric conditions, including major depressive disorder, anxiety

disorders, ADHD, OCD, bulimia nervosa, At Risk Mental State, and post-stroke depression (See eTable).

Five NMAs[e1-3,e5,e6,e9], pooled different types of control conditions (e.g., placebo pill, psychological placebo, sham intervention) into the same node of the network, assuming that these comparators have similar effects. However, this hypothesis should be empirically tested, via meta-regression (when feasible) or subgroup/sensitivity analysis. Only two NMAs did so[e2,e3,e9].

Existing difference between pharmacological and non-pharmacological studies in patient characteristics for baseline disease severity or previous exposure to treatment was reported in only three NMAs[e8,e9,e11], and only one assessed its impact on the results[e9]. The heterogeneity of patient characteristics was unclear or had not been retrieved from primary studies in most of the NMAs.

We found three NMAs[e8,e9,e11] in which the risk of performance or detection bias was not distributed evenly across pharmacological and non-pharmacological studies. Compared to pharmacological trials, those of non-pharmacological interventions were less likely to have participants, care givers and outcome assessors blinded, which is often an unavoidable limitation as some non-pharmacological treatments cannot always be masked. Four NMAs[e1,e2,e10,e11] performed sensitivity analysis to assess the impact of high RoB for lack of blinding on the treatment effects, but for most of the NMAs data were too sparse to draw any conclusion.

Discussion

NMAs combining pharmacological and non-pharmacological interventions for psychiatric conditions may be particularly prone to the violation of the transitivity assumption, which may affect their validity. The definition and classification of the *control*

node in the geometry of the network could impact the results of the NMA. A novel approach, called *component NMA*, could address this issue as it explores the treatment effects of interventions with multiple components.[4] Furthermore, differences in baseline participants characteristics, study RoB and level of blinding may represent a limitation of NMA combining pharmacological and non-pharmacological therapies.[5] Individual Participant Data NMA could overcome these limitations as it allows exploring treatment-patient interactions, to check RoB and obtain extra data from trialists.[6]

We conclude that caution is needed when pharmacological and non-pharmacological interventions are combined in a NMA and specific potential limitations of this type of NMAs should always be systematically and transparently discussed.

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References

1. Mavridis D, Giannatsi M, Cipriani A, et al. A primer on network meta-analysis with emphasis on mental health. Evid Based Ment Health 2015;18:40–6
2. Cortese S, Tomlinson A, Cipriani A. Network Meta-Analyses in Child and Adolescent Psychiatry: A Meta-Review. Journal of the American Academy of Child & Adolescent Psychiatry 2019;58(2):167–179
3. Cope S, Zhang J, Saletan S, Smiechowski B, Jansen JP, Schmid P. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. BMC Med. 2014;12:93.
4. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol 2009; 169:1158e65.
5. Streiner DL, Joffe R. The adequacy of reporting randomized controlled trials in the evaluation of antidepressants. Can. J. Psychiat. 1998; 43: 1026-1030
6. Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, Rovers M. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. PLoS Medicine 2015; 12(7):e1001855