**Network meta-analyses comparing pharmacological and non-pharmacological interventions in psychiatry: Protocol for a meta-review**

**REVIEW QUESTION**

To systematically review and critically appraise network meta-analyses (NMAs) comparing, in the same network, pharmacological and non-pharmacological interventions for psychiatric disorders.

**BACKGROUND**

The role and sequencing of pharmacological *vs.* non-pharmacological interventions is controversial for many psychiatric conditions. Current clinical guidelines provide contrasting recommendations as to whether a pharmacological or non-pharmacological approach should be the first line option for a number of mental health conditions, both in children and in adults. 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, defined as the balance of the distributions of potential effect modifiers related to study design, treatments/controls, outcomes and patient characteristics across all pairwise comparisons.2

Several NMAs have been conducted to estimate the benefits and/or safety of pharmacological or, separately, non-pharmacological interventions for psychiatric disorders.3 An increasing number of NMAs is including pharmacological and non-pharmacological interventions in the same network. The validity of such NMAs is particularly challenging because the transitivity assumption might not hold.

**METHODS**

We will include NMAs comparing, in the same network, any pharmacological, non-pharmacological interventions or combination of them in participants with any mental health condition. We will exclude NMAs of individual participant data.

**Search**

We will search the following electronic databases from the date of database inception to August 2018 with no language/date/typo of document restriction: PubMed (MEDLINE), Ovid (PsycINFO, EMBASE+EMBASE classic, OVID MEDLINE), Web of Knowledge (Web of Science (science citation index expanded), Biological abstracts, BIOSIS, Food science and technology abstracts). We will use the following search terms/strategy:

PUBMED (MEDLINE)

(ADHD OR Attention-Deficit OR attention deficit OR autis\* OR Asperger OR depress\* OR mood OR bipolar OR disruptive mood dysregulation disorder OR anxiety OR anxious OR obsessive compulsive OR OCD OR panic disorder\* OR PTSD OR post traumatic stress disorder OR sleep OR insomnia OR psychotic OR psychosis OR schizophren\* OR conduct disorder\* OR oppositional defiant disorder\* OR anorex\* OR bulim\* OR binge eating OR tic OR tics OR intellectual disabil\* OR mental retardation OR developmental coordination disorder OR learning disorder\* OR substance related disorder\* OR addiction OR addictive) AND (network meta-analy\* OR network metaanaly\* OR indirect treatment meta-analy\* OR indirect treatment metaanaly\* OR mixed treatment comparison\* OR mixed-treatment comparison\* OR indirect comparison meta-analy\* OR  indirect comparison metaanaly\* OR multiple treatment meta-analy\* OR multiple treatment metaanaly\* OR multiple-treatment meta-analy\* OR multiple-treatment metaanaly\* OR indirect meta-analy\* OR indirect metaanaly\* OR indirect treatment comparison\*)

OVID databases

PsycInfo, EMBASE+EMBASE classic, OVID Medline

(ADHD OR Attention-Deficit OR attention deficit OR autism OR autistic OR Asperger OR depression OR depressive OR mood OR bipolar OR disruptive mood dysregulation disorder OR anxiety OR anxious OR obsessive compulsive OR OCD OR panic disorder OR panic disorders OR PTSD OR post traumatic stress disorder OR sleep OR insomnia OR psychotic OR psychosis OR schizophrenia OR schziphrenic OR conduct disorder OR conduct disorders OR oppositional defiant disorder OR oppositional defiant disorders OR anorexia OR anorexic OR bulimia OR bulimic OR binge eating OR tic OR tics OR intellectual disability OR intellectual disabilities OR mental retardation OR developmental coordination disorder OR learning disorder OR learning disorders OR substance related disorder OR substance related disorders OR addiction OR addictive) AND (network meta-analysis network meta-analytic OR network metaanalysis OR indirect treatment meta-analysis OR indirect treatment meta-analytic OR indirect treatment metaanalysis OR mixed treatment comparison OR mixed treatment comparisons OR mixed-treatment comparison OR mixed-treatment comparisons OR indirect comparison meta-analysis OR indirect comparison meta-analytic OR indirect comparison metaanalysis OR indirect comparison metaanalytic OR multiple treatment meta-analysis OR multiple treatment meta-analytic OR multiple treatment metaanalysis OR multiple treatment metaanalytic OR multiple-treatment meta-analysis OR multiple-treatment meta-analytic OR multiple-treatment metaanalysis OR  multiple-treatment metaanalytic OR indirect meta-analysis OR indirect meta-analytic OR indirect metaanalysis OR indirect metaanalytic OR indirect treatment comparison OR indirect treatment comparisons)

WEB OF KNOWLEDGE

(Web of science (science citation index expanded), Biological abstracts, Biosis, Food science and technology abstracts)

ADHD OR Attention-Deficit OR attention deficit OR autis\* OR Asperger OR depress\* OR mood OR bipolar OR disruptive mood dysregulation disorder OR anxiety OR anxious OR obsessive compulsive OR OCD OR panic disorder\* OR PTSD OR post traumatic stress disorder OR sleep OR insomnia OR psychotic OR psychosis OR schizophren\* OR conduct disorder\* OR oppositional defiant disorder\* OR anorex\* OR bulim\* OR binge eating OR tic OR tics OR intellectual disabil\* OR mental retardation OR developmental coordination disorder OR learning disorder\* OR substance related disorder\* OR addiction OR addictive

AND

“network meta-analy\*” OR “network metaanaly\*” OR “indirect treatment meta-analy\*” OR “indirect treatment metaanaly\*” OR “mixed treatment comparison\*” OR “mixed-treatment comparison\*” OR “indirect comparison meta-analy\*” OR  “indirect comparison metaanaly\*” OR “multiple treatment meta-analy\*” OR “multiple treatment metaanaly\*” OR “multiple-treatment meta-analy\*” OR “multiple-treatment metaanaly\*” OR “indirect meta-analy\*” OR “indirect metaanaly\*” OR “indirect treatment comparison\*”

**Study selection and data extraction**

One review author will screen titles and abstracts obtained by the search strategy and will assess the full text of potentially relevant references for inclusion. Any doubt will be solved by discussion with the other reviewers. One reviewer will extract the information from each included study. The data extracted will be checked from the other reviewers. We will extract the following information: design of the studies included in the NMA, type of participants, interventions.

**Data analysis**

We will appraise each NMA based on the approach that Cope and colleagues proposed for assessing the feasibility of performing a valid NMA.4 We will focus on the first two stages: 1) presence of a connected network comparing the treatment of interest for the outcomes of interest and 2) plausibility of the transitivity assumption. In particular, we will evaluate: a) how the control node (or neutral comparator) was defined in the network geometry, b) the differences between pharmacological and non-pharmacological studies with respect to patient characteristics; c) distribution of risk of bias in the network. In accordance with Cope’s approach, we will check if the impact of these issues on results was explored and reported in each of the retained NMA. For the appraisal we will consider NMAs of randomized controlled trials only. Our judgments will be based on the methods reported in the final report of each NMA.

**References**

1. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med. 2013;159(2):130-137.
2. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med. 2013;11:159.
3. 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. In press. DOI: https://doi.org/10.1016/j.jaac.2018.07.891
4. 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.