PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative cardiovascular side effects of medications for attention-deficit/hyperactivity disorder in children, adolescents, and adults: protocol for a systematic review and network meta-analysis
AUTHORS	Lannes, Alice; Farhat, Luis C.; Del Giovane, Cinzia; Cipriani, Andrea; Cortese, Samuele; Revet, Alexis

VERSION 1 – REVIEW

REVIEWER	Bajpai, Ram Keele University, Research Institute of Primary Care and Health Sciences
REVIEW RETURNED	22-Apr-2022

GENERAL COMMENTS	Authors should also adhere the PRISMA-P (or PRISMA protocol) in the preparation of this protocol. Authors can be specific to follow PRISMA NMA for reporting this network meta-analysis. The reference number 16 is for older PRISMA statement, and now PRISMA 2020 can be used when required. It will be good if authors provide some detail on research question (or hypothesis) followed by specific objectives so readers will have more clarity on what has been planned in this systematic review. Are these three outcomes are labelled as main/primary outcomes or anyone of them is a main and others are secondary outcomes. It is important to note that there will be 27 analyses (3 outcomes x 3 time-points x 3 study groups) in this NMA so I am a bit confused that authors will present all 27 analyses in their paper for publication when ready. It is also too much to digest in one paper and how practically challenging to complete review on time. There will many more analyses when you do subgroup/sensitivity analyse. I suggest revisiting to your plan to make it practically achievable and digestible at the same time. I think a MEDLINE search strategy should be attached as s supplementary file with this manuscript. Authors must report the study period with a start and an end date in abstract as well as in the search strategy section. Authors mentioned that NMA would be done in OpenBUGS statistical software that commonly used for Bayesian analysis. Therefore, it is not clear that weather frequentist or Bayesian approach will be used for NMA. Kindly clearly mention what framework will be used for NMA. If it is a Bayesian NMA then title must be updated accordingly. What is the plan for including cluster trials? How unit of analysis will be adjusted in these trials? It should have been described properly. How would you assess the effect of potential effect modifiers methodological or clinical characteristics of the trials? How small study effect will be assessed?

REVIEWER	Ho, Roger C. M. Natl Univ Singapore, Psychological Medicine
REVIEW RETURNED	27-Apr-2022

GENERAL COMMENTS	I have the following comments for the authors to address. 1) Can the authors refer to the following meta-analysis and how is their proposed meta-analysis different from this published study? The Effect of Methylphenidate and Atomoxetine on Heart Rate and Systolic Blood Pressure in Young People and Adults with Attention-Deficit Hyperactivity Disorder (ADHD): Systematic Review, Meta-Analysis, and Meta-Regression. Int J Environ Res Public Health. 2018 Aug 20;15(8):1789. doi: 10.3390/ijerph15081789. PMID: 30127314; PMCID: PMC6121294. 2) Can the authors mention whether fixed or random-effects model was used? Please define fixed and random-effects model and then mention which model was used. fixed-effect model was applied. Fixed-effect models assume that the population effect sizes are the same for all studies. In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung et al 2012). Reference: Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ram Bajpai, Keele University
Comments to the Author:

Thank you for your careful review.

Authors should also adhere the PRISMA-P (or PRISMA protocol) in the preparation of this protocol. Authors can be specific to follow PRISMA NMA for reporting this network meta-analysis. The reference number 16 is for older PRISMA statement, and now PRISMA 2020 can be used when required.

Re: We have included the PRISMA-P and PRISMA-NMA checklists. The page/line numbers of our manuscript where the relevant information can be found are reported in the supplementary material (Supplementary Tables 1 and 2). We have also updated the 2020 reference for PRISMA statement.

It will be good if authors provide some detail on research question (or hypothesis) followed by specific objectives so readers will have more clarity on what has been planned in this systematic review.

Re: This is an exploratory NMA on a topic for which, as we highlighted in the Introduction, available RCTs are characterised by mixed results. Nevertheless, our overarching hypothesis is that, compared to placebo, ADHD medications are more likely to affect the cardiovascular parameters of interest for the present NMA, with differences between psychostimulant and non-psychostimulant agents.

Are these three outcomes are labelled as main/primary outcomes or anyone of them is a main and others are secondary outcomes. It is important to note that there will be 27 analyses (3 outcomes x 3 time-points x 3 study groups) in this NMA so I am a bit confused that authors will present all 27 analyses in their paper for publication when ready. It is also too much to digest in one paper and how practically challenging to complete review on time. There will many more analyses when you do subgroup/sensitivity analyse. I suggest revisiting to your plan to make it practically achievable and digestible at the same time.

Re: We thank the Reviewer for raising this point. All three outcomes are important clinically. We note it is common for NMAs to present a large number of analyses (for instance, Cortese et al., Lancet Psychiatry 2018 included 54 different analyses). This comprehensive approach is one of the strengths of high quality NMAs, that can inform clinical guidelines and policies based on their comprehensive and transparent report. We are confident that a comprehensive and transparent reporting will be possible via the supplemental material. Reader will then have the opportunity to focus their attention on the analyses of interest to them.

I think a MEDLINE search strategy should be attached as s supplementary file with this manuscript.

Re: We note that MEDLINE search syntax is included in the manuscript. Nevertheless, we have added in the supplementary data the search algorithms that we will use for the main other databases.

Authors must report the study period with a start and an end date in abstract as well as in the search strategy section.

Re: We have specified that we will search the databases from their inception. We are not able to predict the exact end date, as we can not predict when exactly the first data extraction will be completed and, hence, when we will run the last update of the search before locking the dataset.

Authors mentioned that NMA would be done in OpenBUGS statistical software that commonly used for Bayesian analysis. Therefore, it is not clear that weather frequentist or Bayesian approach will be used for NMA. Kindly clearly mention what framework will be used for NMA. If it is a Bayesian NMA then title must be updated accordingly.

Re: The reviewer is correct, this information was missing and we have specified in section 2.5.1. that we will perform a frequentist NMA. Due to a change in the choice of the software, considering the recent excellent developments of the R packages for NMA, we will perform all the analyses in R and we have therefore removed the mention of the OpenBUGS software.

What is the plan for including cluster trials? How unit of analysis will be adjusted in these trials? It should have been described properly.

Whether or not to include cluster trial is quite controversial and it depends mainly on the clinical question addressed in the systematic review. While drafting the protocol, we discussed this issue within the review group and in the end we decided not to include cluster trials, because the individual randomization was deemed to be a better design. It is also worth mentioning that the current meta-analysis is based on a large-scale NMA by Cortese et al. published in the Lancet Psychiatry in 2018, which did not identify any clustered trials (so we do not think we are missing any relevant information).

How would you assess the effect of potential effect modifiers methodological or clinical characteristics of the trials? How mall study effect will be assessed?

Re: We will use the Confidence In Network Meta-Analysis (CINeMA) tool to evaluate the confidence of evidence contributing to each network estimate, which takes into account the possible presence of a small study effect.
In addition, as indicated in the manuscript, we will compare the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons, perform NMA meta-regressions and subgroup analysis.

Reviewer: 2
Dr. Roger C. M. Ho, Natl Univ Singapore
Comments to the Author:

I have the following comments for the authors to address.
Thank you for your careful review.

1) Can the authors refer to the following meta-analysis and how is their proposed meta-analysis different from this published study?
The Effect of Methylphenidate and Atomoxetine on Heart Rate and Systolic Blood Pressure in Young People and Adults with Attention-Deficit Hyperactivity Disorder (ADHD): Systematic Review, Meta-Analysis, and Meta-Regression. Int J Environ Res Public Health. 2018 Aug 20;15(8):1789. doi: 10.3390/ijerph15081789. PMID: 30127314; PMCID: PMC6121294.
We thank the Reviewer for asking this clarification. Our meta-analysis will differ from this work in many important aspects, including:
• comparison of many more drugs than just methylphenidate and atomoxetine, since we are assessing the following medications: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, dexmethylphenidate, modafinil and viloxazine;
• more recent update of the literature search and more databases (than just PubMed, EMBASE and ScienceDirect);
• broader range of clinically relevant cardiovascular outcomes, especially diastolic blood pressure and ECG changes;
• we will carry out network meta-analyses (and not just a pairwise meta-analyis).

We have cited the results of this paper in our manuscript (reference 14), as follows: “Liang et al. conducted a pairwise meta-analysis on the effects of methylphenidate and atomoxetine on heart rate and systolic blood pressure [14]. They found that children/adolescents and adults treated with methylphenidate had significant increases in heart rate and systolic blood pressure (post- vs. pre-treatment) compared to placebo, and that children and adolescents treated with atomoxetine had significant increases in the same outcomes compared to those treated with methylphenidate.”

2) Can the authors mention whether fixed or random-effects model was used? Please define fixed and random-effects model and then mention which model was used.
fixed-effect model was applied. Fixed-effect models assume that the population
effect sizes are the same for all studies. In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Cheung et al 2012).
Reference:
Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415

Re: We thank the Reviewer for this reference. As mentioned in several places in the manuscript, we will perform random-effects network meta-analyses.

VERSION 2 – REVIEW

REVIEWER	Bajpai, Ram Keele University, Research Institute of Primary Care and Health Sciences
REVIEW RETURNED	14-Aug-2022

GENERAL COMMENTS	No further comments.

REVIEWER	Ho, Roger C. M. Natl Univ Singapore, Psychological Medicine
REVIEW RETURNED	16-Aug-2022

GENERAL COMMENTS	I recommend publication.