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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

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ABSTRACT

Introduction: Pharmacotherapy is an important component of the multimodal treatment of Attention-deficit/hyperactivity disorder (ADHD). Cardiovascular safety of medications for ADHD are of concern from a clinical and public health standpoint. We aim to conduct a network meta-analysis (NMA) comparing the effects of available medications for ADHD on blood pressure (diastolic and systolic), heart rate, and electrocardiographic parameters over the short and long-term treatment.

Methods and analysis: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for NMAs will be followed. We will include parallel group or cross-over randomised controlled trials (RCTs) conducted in patients with a primary diagnosis of ADHD (no age limits). We will search an extensive number of electronic databases (including MEDLINE, CINAHL, CENTRAL, EMBASE, ERIC, PsycINFO, OpenGrey, Web of Science) and contact study authors/drug manufacturers to gather relevant unpublished information. No language restrictions will be applied. The main outcomes (assessed at 12 weeks, 26 weeks, and 52 weeks) will be: 1) change in diastolic and systolic blood pressure (mmHg); 2) change in heart rate, measured in beats per minute; 3) change in any available electrocardiogram parameters. We will conduct random effects NMA using standardised mean differences with 95% confidence intervals (CIs) for continuous outcomes and odds ratios with 95% CIs for dichotomous outcomes. We will use the Cochrane risk of bias tool-version 2 to assess the risk of bias of included RCTs and the Confidence In Network Meta-Analysis (CINeMA) tool to evaluate the confidence of evidence contributing to each network estimate. Sensitivity analyses will investigate effects at different dose regimens.

Ethics and dissemination: No institutional review board approval will be necessary. The results of this systematic review and meta-analysis will be presented at national and international conferences and published in peer-reviewed journals.

Study registration: PROSPERO – Prospective Register of Systematic Reviews (CRD42021295352).

Keywords: ADHD; Attention-Deficit /Hyperactivity Disorder; cardiovascular; children, adolescents; adults; network meta-analysis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This large-scale and comprehensive network meta-analysis (NMA) comparing ADHD drug treatments in terms of cardiovascular adverse effects, and covering all ages, will increase the estimation of this risk of potentially serious adverse effects. It will allow the available ADHD drugs to be ranked in terms of cardiac acceptability and tolerability, particularly in patients with pre-existing cardiovascular conditions.
- This NMA is timely as it will include viloxazine, an antidepressant which has been recently repurposed as a treatment of ADHD and approved by the Food and Drug Administration (FDA) in 2021. Sensitivity analyses will investigate effects at different dose regimens.
- The results of this NMA will inform clinical decision making and guideline development regarding cardiovascular adverse events, which need to be considered because of the widespread use of ADHD medications and their associated risk of harms.
- As with any evidence synthesis project, the present one will be limited by the amount and quality of the primary studies included in the systematic review.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterised by persistent and impairing inattention and/or hyperactivity/impulsivity that are inappropriate for the developmental level and hinder daily functions [1]. ADHD is the most commonly diagnosed neurodevelopmental disorder, with an estimated worldwide prevalence around 5-7% in school age children [2,3] and 2.5% in adults [4]. Impairing symptoms of ADHD persist in adulthood in around 75% of the cases [5,6]. Several studies across countries (e.g., [7,8]), have highlighted the substantial economic impact of ADHD. The treatment of people with ADHD includes non-pharmacological and pharmacological strategies. Drugs approved by the U.S Food and Drug Administration (FDA) include stimulants (amphetamines and methylphenidate) and non-stimulants (atomoxetine, clonidine, guanfacine extended release, and viloxazine). Medications for ADHD have been found to be efficacious, effective, and generally well tolerated, albeit their use may be associated with undesirable adverse events [9,10].

Although treatment-related adverse events can generally be managed, safety may be a concern for some patients, particularly those with pre-existing cardiovascular conditions [11] because there is some evidence that ADHD medications may impact the cardiovascular system. Indeed, a meta-analysis of randomised controlled trials (RCTs) of stimulants in adults [12] found a mean increase in heart rate of 5.7 beats per minute and a mean increase in systolic blood pressure of 2.0 mm Hg, while abnormal electrocardiographic changes was observed in less than 2% of participants. Vitiello et al. examined the association of stimulant medications with blood pressure and heart rate over 10 years [13]. Even though no significant overall increase in the risk of hypertension over the period was found, stimulants had a persistent adrenergic effect on heart rate during treatment, with greater cumulative stimulant exposure being associated with a higher heart rate at years 3 and 8 of the 10-year follow-up period. However, whether these cardiovascular changes associated with stimulants translate to cardiovascular-related morbidity-mortality is unclear as highlighted by a recent meta-analysis [14] which found no significant association between pharmacological treatment of ADHD and sudden death, stroke, myocardial infarction or death from any cause (although only eight studies were

included and some estimates were relatively imprecise with some of the confidence intervals failing to exclude important harm, in particular for sudden death/arrhythmia).

Despite the increasing evidence on the cardiovascular effects of ADHD medications as a group, limited research has evaluated the comparative effects of ADHD medications in the cardiovascular system, which could inform clinical decision making. In their previous network meta-analysis (NMA) of RCTs of ADHD medications, Cortese et al. [15] compared amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo in terms of their impact on diastolic and systolic pressure. However, they did not evaluate the comparative effects of ADHD medications on electrocardiographic (ECG) parameters and heart rate, which could be crucial to gain insight into the cardiovascular effects, and hence, the possible harms of these medications. Furthermore, the FDA approved viloxazine for the treatment of ADHD in 2021, and this medication was not included in the original NMA. The present paper reports the protocol of a NMA aimed to fill these gaps by comparing the cardiovascular effects of currently available medications for ADHD on diastolic and systolic blood pressure, ECG parameters and heart rate.

2. Materials and Methods

Methods for this systematic review and meta-analysis were developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16] and has been registered within PROSPERO (CRD42021295352).

2.1. Selection criteria

2.1.1. Population

Inclusion criteria

We will focus on RCTs, conducted in outpatient or inpatient setting, of children (≥5 and <12 years), adolescents (≥12 and <18 years) or adults (≥18 years) with a primary diagnosis of ADHD as per Diagnostic and Statistical Manual of Mental Disorders (DSM; DSM-III, DSM III-R, DSM-IV-TR, DSM- 5) or per International Classification of Diseases (ICD; ICD-11) or the equivalent diagnosis of

Hyperkinetic Syndrome as ICD-9 and ICD-10. Gender, ADHD subtype or clinical features, intelligence quotient (IQ) and socio-economic status of participants will not be restrictive criteria for inclusion.

Exclusion criteria

We will exclude studies that recruited participants with:

1. The equivalent diagnosis of ADHD based on DSM-II criteria, as these were not standardized criteria;
2. A diagnosis of Minimal Brain Dysfunction, which is not comparable to DSM definitions of ADHD or ICD-9 and 10 definitions of Hyperkinetic Syndrome;
3. ADHD comorbid with a genetic syndrome (such as Fragile X syndrome, Tuberous sclerosis complex, or Velo-cardio-facial/DiGeorge syndrome);
4. "Hyperkinesis" or "hyperactivity" not meeting standardized diagnostic criteria;
5. ADHD pharmacological treatment prior to entering the study, unless participants completed an appropriate washout period before starting the study (Table 1);
6. Previous response to the same medication tested in the randomised phase (irrespective of washout period) or with a definition of "responders" or "stabilized/optimized" to an ADHD medication during a run-in/open label phase prior to randomisation (irrespective of washout period);
7. "Resistance" (as defined in the selected articles) to a previous ADHD drug.

Table 1. Washout periods.

Drug	Washout (days)
Methylphenidate	1
Amphetamine derivatives	3-5
Lisdexamfetamine dimesylate	2-3
Atomoxetine	1
Clonidine	3
Guanfacine	3-4
Bupropion	2-4
Modafinil	3-4
Viloxazine	4

2.1.2. Interventions and exposures

We will focus on any of the following medications as oral monotherapy, compared to each other or with placebo: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, dexmethylphenidate, modafinil and viloxazine. Possible comparators used in RCTs will be either a placebo or another ADHD medication.

2.1.3. Outcomes

We will focus on the three following outcomes:

1. Change in blood pressure (diastolic and systolic blood pressure), measured in mmHg;
2. Change in heart rate, measured in beats per minute;
3. Change in any reported electrocardiogram (ECG) parameters.

Timing of outcome assessment

We will evaluate these outcomes at the time points closest 12 weeks (short term), 26 weeks (medium term) and 52 weeks (long term).

2.1.4. Type of studies

We will include double-blinded RCTs. Quasi-randomised controlled trials, studies using Latin square approach without adequate randomisation, open-label or single blind RCTs, and N-of-1 trials will be excluded. Both parallel group and crossover trials will be eligible. To address concerns around possible carry-over effects in cross-over trials, we will use data from the pre-crossover phase. When pre-crossover data are not reported, we will contact study authors to gather them. If those data are not available, we will use data at the endpoint (after crossing over), only if there was an appropriate washout period between the two phases of the trial (Table 1). Data from the withdrawal phase of a discontinuation trial (with subjects already treated, randomised to continuation or placebo) will only be used if subjects were not stabilized during the open-label phase or if there was a washout period before randomisation to the continuation phase. We will exclude long-term studies using a maintenance design,

2.2. Search strategy

2.2.1. Electronic searches

We will search the following electronic databases: PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations and Theses (UK and Ireland), ProQuest Dissertations and Theses (abstracts and international), and the WHO International Trials Registry Platform, including ClinicalTrials.gov. No language restrictions will be applied.

We will use the search terms “adhd” OR “hkd” OR “addh” OR “hyperkine*” OR “attention deficit*” OR “hyper-activ*” OR “hyperactiv*” OR “overactive” OR “inattentive” OR “impulsiv*” combined with a list of terms for ADHD medications, adapted for each database. The search strategy will build on the one used in Cortese et al. [15,17] (PROSPERO CRD42014008976) and will additionally include search terms for RCTs of viloxazine for ADHD. We will include relevant data from the RCTs included in Cortese et al. and update the search to retrieve any relevant RCT published after the last search in Cortese et al. (i.e., April 7th, 2017). Of note, we will check if any RCT on viloxazine for ADHD was published before the date of the last search in Cortese et al. [15]).

As an example, the search terms and syntax we will use for PubMed will be as follows: ("Attention Deficit Disorder with Hyperactivity"[Mesh] OR adhd[tiab] OR hkd[tiab] OR addh[tiab] OR hyperkine*[tiab] OR "attention deficit*"[tiab] OR hyper-activ*[tiab] OR hyperactiv*[tiab] OR overactive[tiab] OR inattentive[tiab] OR impulsiv*[tiab]) AND ("Amphetamines"[Mesh] OR "Bupropion"[Mesh] OR "Clonidine"[Mesh] OR "Methylphenidate"[Mesh] OR "Dexmethylphenidate"[Mesh] OR "Guanfacine"[Mesh] OR Adderall[tiab] OR Amphetamine[tiab] OR Desoxyn*[tiab] OR Phenopromin[tiab] OR Amfetamine[tiab] OR Phenamine[tiab] OR Centramina[tiab] OR Fenamine[tiab] OR Levoamphetamine[tiab] OR Dexamfetamine[tiab] OR Dexamphetamine[tiab] OR Dexedrine[tiab] OR Dextroamphetamine[tiab] OR DextroStat[tiab] OR Oxydess[tiab] OR Methylamphetamine[tiab] OR Methylenedioxyamphetamine[tiab] OR Methamphetamine[tiab] OR Chloroamphetamine[tiab] OR Metamfetamine[tiab] OR Deoxyephedrine[tiab] OR Desoxyephedrine[tiab] OR Ecstasy[tiab] OR Atomoxetine[tiab] OR

Biphentin[tiab] OR Bupropion[tiab] OR Amfebutamone[tiab] OR Zyntabac[tiab] OR Quomen[tiab] OR Wellbutrin[tiab] OR Zyban[tiab] OR Catapres*[tiab] OR Clonidine[tiab] OR Klofenil[tiab] OR Clofenil[tiab] OR Chlophazolin[tiab] OR Gemiton[tiab] OR Hemiton[tiab] OR Isoglaucon[tiab] OR Klofelin[tiab] OR Clopheline[tiab] OR Clofelin[tiab] OR Dixarit[tiab] OR Concerta[tiab] OR Daytrana[tiab] OR Methylphenidate[tiab] OR Equasym[tiab] OR Methylin[tiab] OR Tsentedrin[tiab] OR Centedrin[tiab] OR Phenidylate[tiab] OR Ritalin*[tiab] OR Duraclon[tiab] OR Elvanse[tiab] OR Focalin[tiab] OR Dexmethylphenidate[tiab] OR Guanfacine[tiab] OR Estulic[tiab] OR Tenex[tiab] OR Kapvay[tiab] OR Lisdexamfetamine[tiab] OR Vyvanse[tiab] OR Medikinet[tiab] OR Metadate[tiab] OR Modafinil[tiab] OR Nexiclon[tiab] OR Quillivant[tiab] OR Strattera[tiab] OR Viloxazine[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])

2.2.2.Other sources

We will also search the US FDA, European Medicines Agency (EMA), and relevant drug manufacturers' websites, as well as references of previous systematic reviews and guidelines, to retrieve any additional pertinent RCT. We will also systematically contact study authors and drug manufacturers to gather relevant unpublished information and data.

2.2.3.Selection of studies

Electronic and manual searches will identify studies which will be indexed in Zotero with their citations, titles and abstracts; duplicates will then be identified and merged using the dedicated functions of Zotero software. The eligibility for inclusion process will be conducted in two separate stages:

1. The search will be conducted by a professional company (Systematic Review Solutions Ltd., SRS). Two reviewers (AL and LF) will independently perform screen titles/abstracts and will exclude those not pertinent. A final list will be agreed with discrepancies resolved by consensus between the two authors. When consensus is not reached, any disagreement will be

resolved by discussion with one senior author (SC). If any doubt about inclusion exists, the article will proceed to the next stage.

2. The full-text version of the articles passing the first stage of screening will be assessed for eligibility by two authors (AL and LF), independently. Discrepancies will be resolved by consensus between the two authors and, if needed, one senior author (SC) will act as arbitrator. Data from multiple reports of the same study will be linked together. Where required, we will contact the corresponding author to inquire on study eligibility. Missing data will be obtained from the authors wherever possible via e-mail contacts.

2.3. Data extraction

The following information will be collected in an Excel spreadsheet from each included study:

- Publication details: Study citation, year of publication, country where the study was conducted;
- General study characteristics: year(s) of study, setting, number of centres, design (type of RCT), sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Characteristics of study participants: gender distribution, mean and range of age, presence and type of co-morbid (neuro)psychiatric conditions, mean (and standard deviation [SD]) IQ, number randomised into each group with number of dropouts, and whether patients were naïve of ADHD medications at baseline or previously exposed to other ADHD medications;
- Characteristics of interventions: mean and maximum doses, formulation, add-on interventions (if any), and whether forced dose or optimized treatment;
- Time(s) of outcome measurement;
- Reported outcome measures: diastolic and systolic blood pressure, heart rate, and any other available cardiovascular parameter, including ECG parameters;
- Type of analysis: intention-to-treat or per protocol.

2.4. Assessment of study quality and risk of bias

We will assess the risk of bias of each individual RCT using the Cochrane risk of bias-2 [18]. This tool is structured into five domains through which bias might be introduced into the result, which focus on different aspects of design, conduct and reporting. We will use the proposed algorithm by the Cochrane group which generates a judgment about the risk of bias related to each domain and overall study and can be 'Low' or 'High' risk of bias or can express 'Some concerns'.

2.5. Data analysis

2.5.1.Synthesis of results and measure of treatment effect

We will conduct pairwise meta-analyses (active drug vs placebo, or active drug vs another active drug) in R (version 4.1.2) and NMAs in OpenBUGS (version 3.2.3) via random effects model using standardised mean differences (SMDs, Cohen's d) with 95% confidence intervals (CIs) for continuous outcomes and odds ratios (ORs) with 95% CIs for dichotomous outcomes (e.g., binary variables in ECG parameter changes). We will conduct all analyses separately for studies in children /adolescents and for studies in adults. The primary analysis will be restricted to studies using medications within the therapeutic range, as per FDA recommendations, where applicable.

2.5.2.Statistical analysis

Missing dichotomous outcome data will be managed according to the intention-to-treat principle (participants in the full analysis set who dropped out after randomisation will be considered to have had a negative outcome). Missing continuous outcome data will be analysed using last observation carried forward to the final assessment (LOCF) if LOCF data were reported. Published SD will be used where available, and if they are not available, they will be calculated from p-values, t-values, CIs or standard errors. If these values are missing, attempts will be made to obtain these data from trial authors and if unsuccessful, a validated method for imputation of SD will be used [19].

To assess transitivity assumption, we will compare the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons. A common estimate for the heterogeneity variance will be assumed for all comparisons in the entire network, and

we will assess the presence of statistical heterogeneity using the magnitude of the heterogeneity variance parameter ($\tau 2$) and total I^2 statistic. Incoherence between direct and indirect sources of evidence will be statistically assessed globally, by comparison of the fit and parsimony of consistency and inconsistency models [20], and locally, by calculation of the difference between direct and indirect estimates in all closed loops in the network [21]. The node splitting method, which separates evidence on a particular comparison into direct and indirect evidence, will be used to calculate the inconsistency of the model. We will estimate the ranking probabilities of being at each possible rank for each intervention. The treatment hierarchy will be summarized and reported as surface under the cumulative ranking curve [22]. To determine whether the results are affected by possible effect modifiers, we will conduct a network meta-regression for outcomes according to the following variables: study sponsorship, treatment duration, comorbid psychiatric disorders, study risk of bias, mean baseline severity, and percentage of participants treated with stable doses of medications in RCTs.

The Confidence In Network Meta-Analysis (CINeMA) software will be used to assess the confidence of evidence contributing to each network estimate [23]. This tool is based on a methodological framework which shows how much information each study contributes to the results from NMA by considering six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.

2.5.3. Additional analyses

We will investigate effects at different dose regimens in two sets of sensitivity analyses: 1) we will exclude studies that did not use the FDA-licensed dose; 2) we will include studies in which the dose ranges used were recommended in national or international guidelines or formularies but differed from FDA recommendations. Finally, to investigate possible differences between lisdexamfetamine and other amphetamines, we will conduct a subgroup analysis separating lisdexamfetamine from the other amphetamines.

2.6. Patient and public involvement

We contacted representatives of the ADHD Foundation, a major charity on ADHD in the UK, who confirmed: the relevance of the topic; the appropriateness of the outcomes chosen; and their willingness to contribute to disseminate the study findings. As this is a protocol, no patients were directly involved in the study.

3. Ethics and dissemination

No ethical problems are anticipated in the conduct of this meta-analysis. Project findings will be disseminated in the form of original articles in peer-reviewed scientific journals and in the form of oral communications at national and international conferences of (child and adolescent) psychiatry, psychology, and paediatrics. The full dataset of the NMA and the codes for the analyses will be available online in open access in Mendeley Data, a secure online repository for research data.

4. Registration of the protocol, timeline of the study and planned contributions to the meta-analysis

The protocol of this NMA protocol has been registered in PROSPERO on 30 November 2021 (CRD42021295352). Preliminary research began in January 2022 and the systematic search and selection process will begin in April 2022, with the aim of starting data extraction in July 2022. Data analysis is expected to be completed in January 2023.

AL and LF will conduct the literature search and screen articles to select and retain those that meet the inclusion criteria. When consensus is not reached, SC will arbitrate the discrepancies between these two researchers regarding the decision to include or not the article concerned. AL and LF will read in depth the included papers and extract the data. AL and CDG will carry out the statistical analysis. SC, AR and AC will provide expertise on issues related to (child and adolescent) psychiatry as well as the interpretation of results and their implications. AL and AR will draft the first version of the article and SC will further edit it. All authors will contribute to and approve the final manuscript.

Declarations

Contributions of authors' statement

AL, SC, AR and AC designed the protocol. AL, AR and SC produced the first draft of the manuscript. All other co-authors critically reviewed the protocol and substantively edited all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

Samuele Cortese declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. LF receives scholarship support from grant #2021/08540-0, São Paulo Research Foundation (FAPES).

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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

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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

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ABSTRACT

Introduction: Pharmacotherapy is an important component of the multimodal treatment of Attention-deficit/hyperactivity disorder (ADHD). Cardiovascular safety of medications for ADHD are of concern from a clinical and public health standpoint. We aim to conduct a network meta-analysis (NMA) comparing the effects of available medications for ADHD on blood pressure (diastolic and systolic), heart rate, and electrocardiographic parameters over the short and long-term treatment.

Methods and analysis: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for protocols and NMAs will be followed. We will include parallel group or cross-over randomised controlled trials (RCTs) conducted in patients with a primary diagnosis of ADHD (no age limits). We will search an extensive number of electronic databases (including MEDLINE, CINAHL, CENTRAL, EMBASE, ERIC, PsycINFO, OpenGrey, Web of Science) from their inception and contact study authors/drug manufacturers to gather relevant unpublished information. No language restrictions will be applied. The main outcomes (assessed at 12 weeks, 26 weeks, and 52 weeks) will be: 1) change in diastolic and systolic blood pressure (mmHg); 2) change in heart rate, measured in beats per minute; 3) change in any available electrocardiogram parameters. We will conduct random effects NMA using standardised mean differences with 95% confidence intervals (CIs) for continuous outcomes and odds ratios with 95% CIs for dichotomous outcomes. We will use the Cochrane risk of bias tool-version 2 to assess the risk of bias of included RCTs and the Confidence In Network Meta-Analysis (CINeMA) tool to evaluate the confidence of evidence contributing to each network estimate. Sensitivity analyses will investigate effects at different dose regimens.

Ethics and dissemination: No institutional review board approval will be necessary. The results of this systematic review and meta-analysis will be presented at national and international conferences and published in peer-reviewed journals.

Study registration: PROSPERO – Prospective Register of Systematic Reviews (CRD42021295352).

Keywords: ADHD; Attention-Deficit /Hyperactivity Disorder; cardiovascular; children, adolescents; adults; network meta-analysis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- *This networked meta-analysis (NMA) will be coordinated by clinicians and statisticians with a solid expertise in ADHD and in the state-of-the-art statistical analyses required for a NMA.*
- *We will systematically include both published and unpublished data, gathered from study authors or from drug manufacturers.*
- *This NMA will include viloxazine, which has been approved by the Food and Drug Administration (FDA) in 2021 for the treatment of ADHD.*
- *Sensitivity analyses will assess effects at different dose regimens.*
- *As with any meta-analysis, the present one will be limited by the amount and quality of the primary included studies*

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterised by persistent and impairing inattention and/or hyperactivity/impulsivity that are inappropriate for the developmental level and hinder daily functions [1]. ADHD is the most commonly diagnosed neurodevelopmental disorder, with an estimated worldwide prevalence around 5-7% in school age children [2,3] and 2.5% in adults [4]. Impairing symptoms of ADHD persist in adulthood in around 75% of the cases [5,6]. Several studies across countries (e.g., [7,8]), have highlighted the substantial economic impact of ADHD. The treatment of people with ADHD includes non-pharmacological and pharmacological strategies. Drugs approved by the U.S Food and Drug Administration (FDA) include stimulants (amphetamines and methylphenidate) and non-stimulants (atomoxetine, clonidine, guanfacine extended release, and viloxazine). Medications for ADHD have been found to be efficacious, effective, and generally well tolerated, albeit their use may be associated with undesirable adverse events [9,10].

Although treatment-related adverse events can generally be managed, safety may be a concern for some patients, particularly those with pre-existing cardiovascular conditions [11] because there is some evidence that ADHD medications may impact the cardiovascular system. Indeed, a meta-analysis of randomised controlled trials (RCTs) of stimulants in adults [12] found a mean increase in heart rate of 5.7 beats per minute and a mean increase in systolic blood pressure of 2.0 mm Hg, while abnormal electrocardiographic changes was observed in less than 2% of participants. Vitiello et al. examined the association of stimulant medications with blood pressure and heart rate over 10 years [13]. Even though no significant overall increase in the risk of hypertension over the period was found, stimulants had a persistent adrenergic effect on heart rate during treatment, with greater cumulative stimulant exposure being associated with a higher heart rate at years 3 and 8 of the 10-year follow-up period. 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. However, whether these cardiovascular changes associated with stimulants translate to cardiovascular-related morbidity-mortality is unclear as highlighted by a recent meta-analysis [15] which found no significant association between pharmacological treatment of ADHD and sudden death, stroke, myocardial infarction or death from any cause (although only eight studies were included and some estimates were relatively imprecise with some of the confidence intervals failing to exclude important harm, in particular for sudden death/arrhythmia).

Despite the increasing evidence on the cardiovascular effects of ADHD medications as a group, limited research has evaluated the comparative effects of ADHD medications in the cardiovascular system, which could inform clinical decision making. In their previous network meta-analysis (NMA) of RCTs of ADHD medications, Cortese et al. [16] compared amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo in terms of their impact on diastolic and systolic pressure. However, they did not evaluate the comparative effects of ADHD medications on electrocardiographic (ECG) parameters and heart rate, which could be crucial to gain insight into the cardiovascular effects, and hence, the possible harms of these medications. Furthermore, the FDA approved viloxazine for the treatment of ADHD in 2021, and this medication was not included in the original NMA. The present paper reports the protocol of a NMA aimed to fill these gaps by comparing the cardiovascular effects of currently available medications for ADHD on diastolic and systolic blood pressure, ECG parameters and heart rate.

2. Materials and Methods

Methods for this systematic review and meta-analysis were developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [17] for systematic review Protocols (PRISMA-P) [18,19] and for Network Meta-Analyses (PRISMA-NMA) [20], with the corresponding checklists presented in the supplementary data (Supplementary Tables 1 and 2). The protocol has been registered within PROSPERO (CRD42021295352).

2.1. Selection criteria

2.1.1. Population

Inclusion criteria

We will focus on RCTs, conducted in outpatient or inpatient setting, of children (≥5 and <12 years), adolescents (≥12 and <18 years) or adults (≥18 years) with a primary diagnosis of ADHD as per Diagnostic and Statistical Manual of Mental Disorders (DSM; DSM-III, DSM III-R, DSM-IV-TR, DSM- 5) or per International Classification of Diseases (ICD; ICD-11) or the equivalent diagnosis of Hyperkinetic Syndrome as ICD-9 and ICD-10. Gender, ADHD subtype or clinical features, intelligence quotient (IQ) and socio-economic status of participants will not be restrictive criteria for inclusion.

Exclusion criteria

We will exclude studies that recruited participants with:

1. The equivalent diagnosis of ADHD based on DSM-II criteria, as these were not standardized criteria;
2. A diagnosis of Minimal Brain Dysfunction, which is not comparable to DSM definitions of ADHD or ICD-9 and 10 definitions of Hyperkinetic Syndrome;
3. ADHD comorbid with a genetic syndrome (such as Fragile X syndrome, Tuberous sclerosis complex, or Velo-cardio-facial/DiGeorge syndrome);
4. “Hyperkinesis” or “hyperactivity” not meeting standardized diagnostic criteria;
5. ADHD pharmacological treatment prior to entering the study, unless participants completed an appropriate washout period before starting the study (Table 1);
6. Previous response to the same medication tested in the randomised phase (irrespective of washout period) or with a definition of “responders” or “stabilized/optimized” to an ADHD medication during a run-in/open label phase prior to randomisation (irrespective of washout period);
7. “Resistance” (as defined in the selected articles) to a previous ADHD drug.

Table 1. Washout periods.

Drug	Washout (days)
Methylphenidate	1
Amphetamine derivatives	3-5
Lisdexamfetamine dimesylate	2-3
Atomoxetine	1
Clonidine	3
Guanfacine	3-4
Bupropion	2-4
Modafinil	3-4
Viloxazine	4

2.1.2. Interventions and exposures

We will focus on any of the following medications as oral monotherapy, compared to each other or with placebo: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, dexmethylphenidate, modafinil and viloxazine. Possible comparators used in RCTs will be either a placebo or another ADHD medication.

2.1.3. Outcomes

We will focus on the three following outcomes:

1. Change in blood pressure (diastolic and systolic blood pressure), measured in mmHg;
2. Change in heart rate, measured in beats per minute;
3. Change in any reported electrocardiogram (ECG) parameters.

Timing of outcome assessment

We will evaluate these outcomes at the time points closest 12 weeks (short term), 26 weeks (medium term) and 52 weeks (long term).

2.1.4. Type of studies

We will include double-blinded RCTs. Quasi-randomised controlled trials, studies using Latin square approach without adequate randomisation, open-label or single blind RCTs, and N-of-1 trials will be excluded. Both parallel group and crossover trials will be eligible. To address concerns around possible carry-over effects in cross-over trials, we will use data from the pre-crossover phase. When

pre-crossover data are not reported, we will contact study authors to gather them. If those data are not available, we will use data at the endpoint (after crossing over), only if there was an appropriate washout period between the two phases of the trial (Table 1). Data from the withdrawal phase of a discontinuation trial (with subjects already treated, randomised to continuation or placebo) will only be used if subjects were not stabilized during the open-label phase or if there was a washout period before randomisation to the continuation phase. We will exclude long-term studies using a maintenance design,

2.2. Search strategy

2.2.1. Electronic searches

We will search the following electronic databases from their inception: PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations and Theses (UK and Ireland), ProQuest Dissertations and Theses (abstracts and international), and the WHO International Trials Registry Platform, including ClinicalTrials.gov. No language restrictions will be applied.

We will use the search terms “adhd” OR “hkd” OR “addh” OR “hyperkine*” OR “attention deficit*” OR “hyper-activ*” OR “hyperactiv*” OR “overactive” OR “inattentive” OR “impulsiv*” combined with a list of terms for ADHD medications, adapted for each database. The search strategy will build on the one used in Cortese et al. [16,21] (PROSPERO CRD42014008976) and will additionally include search terms for RCTs of viloxazine for ADHD. We will include relevant data from the RCTs included in Cortese et al. and update the search to retrieve any relevant RCT published after the last search in Cortese et al. (i.e., April 7th, 2017). Of note, we will check if any RCT on viloxazine for ADHD was published before the date of the last search in Cortese et al. [16]).

As an example, the search terms and syntax we will use for PubMed will be as follows (for the specific syntax for each database, see online Appendix):

("Attention Deficit Disorder with Hyperactivity"[Mesh] OR adhd[tiab] OR hkd[tiab] OR addh[tiab] OR hyperkine*[tiab] OR "attention deficit*"[tiab] OR hyper-activ*[tiab] OR hyperactiv*[tiab] OR

overactive[tiab] OR inattentive[tiab] OR impulsiv*[tiab]) AND ("Amphetamines"[Mesh] OR "Bupropion"[Mesh] OR "Clonidine"[Mesh] OR "Methylphenidate"[Mesh] OR "Dexmethylphenidate"[Mesh] OR "Guanfacine"[Mesh] OR Adderall[tiab] OR Amphetamine[tiab] OR Desoxyn*[tiab] OR Phenopromin[tiab] OR Amfetamine[tiab] OR Phenamine[tiab] OR Centramina[tiab] OR Fenamine[tiab] OR Levoamphetamine[tiab] OR Dexamfetamine[tiab] OR Dexamphetamine[tiab] OR Dexedrine[tiab] OR Dextroamphetamine[tiab] OR DextroStat[tiab] OR Oxydess[tiab] OR Methylamphetamine[tiab] OR Methylenedioxyamphetamine[tiab] OR Methamphetamine[tiab] OR Chloroamphetamine[tiab] OR Metamfetamine[tiab] OR Deoxyephedrine[tiab] OR Desoxyephedrine[tiab] OR Ecstasy[tiab] OR Atomoxetine[tiab] OR Biphentin[tiab] OR Bupropion[tiab] OR Amfebutamone[tiab] OR Zyntabac[tiab] OR Quomen[tiab] OR Wellbutrin[tiab] OR Zyban[tiab] OR Catapres*[tiab] OR Clonidine[tiab] OR Klofenil[tiab] OR Clofenil[tiab] OR Chlophazolin[tiab] OR Gemiton[tiab] OR Hemiton[tiab] OR Isoglaucon[tiab] OR Klofelin[tiab] OR Clopheline[tiab] OR Clofelin[tiab] OR Dixarit[tiab] OR Concerta[tiab] OR Daytrana[tiab] OR Methylphenidate[tiab] OR Equasym[tiab] OR Methylin[tiab] OR Tsentedrin[tiab] OR Centedrin[tiab] OR Phenidylate[tiab] OR Ritalin*[tiab] OR Duraclon[tiab] OR Elvanse[tiab] OR Focalin[tiab] OR Dexmethylphenidate[tiab] OR Guanfacine[tiab] OR Estulic[tiab] OR Tenex[tiab] OR Kapvay[tiab] OR Lisdexamfetamine[tiab] OR Vyvanse[tiab] OR Medikinet[tiab] OR Metadate[tiab] OR Modafinil[tiab] OR Nexiclon[tiab] OR Quillivant[tiab] OR Strattera[tiab] OR Viloxazine[tiab] OR Qelbree[tiab] OR Vivalan[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])

2.2.2. Other sources

We will also search the US FDA, European Medicines Agency (EMA), and relevant drug manufacturers' websites, as well as references of previous systematic reviews and guidelines, to retrieve any additional pertinent RCT. We will also systematically contact study authors and drug manufacturers to gather relevant unpublished information and data.

2.2.3.Selection of studies

Electronic and manual searches will identify studies which will be indexed in Zotero with their citations, titles and abstracts; duplicates will then be identified and merged using the dedicated functions of Zotero software. The eligibility for inclusion process will be conducted in two separate stages:

1. The search will be conducted by a professional company (Systematic Review Solutions Ltd., SRS). Two reviewers (AL and LF) will independently perform screen titles/abstracts and will exclude those not pertinent. A final list will be agreed with discrepancies resolved by consensus between the two authors. When consensus is not reached, any disagreement will be resolved by discussion with one senior author (SC). If any doubt about inclusion exists, the article will proceed to the next stage.
2. The full-text version of the articles passing the first stage of screening will be assessed for eligibility by two authors (AL and LF), independently. Discrepancies will be resolved by consensus between the two authors and, if needed, one senior author (SC) will act as arbitrator. Data from multiple reports of the same study will be linked together. Where required, we will contact the corresponding author to inquire on study eligibility. Missing data will be obtained from the authors wherever possible via e-mail contacts.

2.3. Data extraction

The following information will be collected in an Excel spreadsheet from each included study:

- Publication details: Study citation, year of publication, country where the study was conducted;
- General study characteristics: year(s) of study, setting, number of centres, design (type of RCT), sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Characteristics of study participants: gender distribution, mean and range of age, presence and type of co-morbid (neuro)psychiatric conditions, mean (and standard deviation [SD]) IQ, number randomised into each group with number of dropouts, and whether patients were naïve of ADHD medications at baseline or previously exposed to other ADHD medications;

- Characteristics of interventions: mean and maximum doses, formulation, add-on interventions (if any), and whether forced dose or optimized treatment;
- Time(s) of outcome measurement;
- Reported outcome measures: diastolic and systolic blood pressure, heart rate, and any other available cardiovascular parameter, including ECG parameters;
- Type of analysis: intention-to-treat or per protocol.

2.4. Assessment of study quality and risk of bias

We will assess the risk of bias of each individual RCT using the Cochrane risk of bias-2 [22]. This tool is structured into five domains through which bias might be introduced into the result, which focus on different aspects of design, conduct and reporting. We will use the proposed algorithm by the Cochrane group which generates a judgment about the risk of bias related to each domain and overall study and can be 'Low' or 'High' risk of bias or can express 'Some concerns'.

2.5. Data analysis

2.5.1. Synthesis of results and measure of treatment effect

We will conduct pairwise meta-analyses (active drug vs placebo, or active drug vs another active drug) and frequentist NMAs in R (version 4.2.1.) via random effects model using standardised mean differences (SMDs, Cohen's d) with 95% confidence intervals (CIs) for continuous outcomes and odds ratios (ORs) with 95% CIs for dichotomous outcomes (e.g., binary variables in ECG parameter changes). We will conduct all analyses separately for studies in children /adolescents and for studies in adults. The primary analysis will be restricted to studies using medications within the therapeutic range, as per FDA recommendations, where applicable.

2.5.2.Statistical analysis

Missing dichotomous outcome data will be managed according to the intention-to-treat principle (participants in the full analysis set who dropped out after randomisation will be considered to have had a negative outcome). Missing continuous outcome data will be analysed using last observation carried forward to the final assessment (LOCF) if LOCF data were reported. Published SD will be used where available, and if they are not available, they will be calculated from p-values, t-values, CIs or standard errors. If these values are missing, attempts will be made to obtain these data from trial authors and if unsuccessful, a validated method for imputation of SD will be used [23].

To assess transitivity assumption, we will compare the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons. A common estimate for the heterogeneity variance will be assumed for all comparisons in the entire network, and we will assess the presence of statistical heterogeneity using the magnitude of the heterogeneity variance parameter ($\tau 2$) and total I^2 statistic. Incoherence between direct and indirect sources of evidence will be statistically assessed globally, by comparison of the fit and parsimony of consistency and inconsistency models [24], and locally, by calculation of the difference between direct and indirect estimates in all closed loops in the network [25]. The node splitting method, which separates evidence on a particular comparison into direct and indirect evidence, will be used to calculate the inconsistency of the model. We will estimate the ranking probabilities of being at each possible rank for each intervention. The treatment hierarchy will be summarized and reported as surface under the cumulative ranking curve [26]. To determine whether the results are affected by possible effect modifiers, we will conduct a network meta-regression for outcomes according to the following variables: study sponsorship, treatment duration, comorbid psychiatric disorders, study risk of bias, mean baseline severity, and percentage of participants treated with stable doses of medications in RCTs.

The Confidence In Network Meta-Analysis (CINeMA) software will be used to assess the confidence of evidence contributing to each network estimate [27]. This tool is based on a methodological framework which shows how much information each study contributes to the results

from NMA by considering six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.

2.5.3. Additional analyses

We will investigate effects at different dose regimens in two sets of sensitivity analyses: 1) we will exclude studies that did not use the FDA-licensed dose; 2) we will include studies in which the dose ranges used were recommended in national or international guidelines or formularies but differed from FDA recommendations. Finally, to investigate possible differences between lisdexamfetamine and other amphetamines, we will conduct a subgroup analysis separating lisdexamfetamine from the other amphetamines.

2.6. Patient and public involvement

We contacted representatives of the ADHD Foundation, a major charity on ADHD in the UK, who confirmed: the relevance of the topic; the appropriateness of the outcomes chosen; and their willingness to contribute to disseminate the study findings. As this is a protocol, no patients were directly involved in the study.

3. Ethics and dissemination

No ethical problems are anticipated in the conduct of this meta-analysis. Project findings will be disseminated in the form of original articles in peer-reviewed scientific journals and in the form of oral communications at national and international conferences of (child and adolescent) psychiatry, psychology, and paediatrics. The full dataset of the NMA and the codes for the analyses will be available online in open access in Mendeley Data, a secure online repository for research data.

4. Registration of the protocol, timeline of the study and planned contributions to the meta-analysis

The protocol of this NMA protocol has been registered in PROSPERO on 30 November 2021 (CRD42021295352). Preliminary research began in January 2022 and the systematic search and selection process began in April 2022.

AL and LF will conduct the literature search and screen articles to select and retain those that meet the inclusion criteria. When consensus is not reached, SC will arbitrate the discrepancies between these two researchers regarding the decision to include or not the article concerned. AL and LF will read in depth the included papers and extract the data. AL and CDG will carry out the statistical analysis. SC, AR and AC will provide expertise on issues related to (child and adolescent) psychiatry as well as the interpretation of results and their implications. AL and AR will draft the first version of the article and SC will further edit it. All authors will contribute to and approve the final manuscript.

Declarations

Contributions of authors' statement

AL, SC, AR and AC designed the protocol which was critically reviewed by LCF and CDG. AL, AR and SC produced the first draft of the manuscript. AC, LCF and CDG substantively edited all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

Samuele Cortese declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. LF receives scholarship support from grant #2021/08540-0, São Paulo Research Foundation (FAPES).

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Supplemental material

Supplementary Table 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*.

Section and topic	Item No	Checklist item	Reported on page (with quotes from the text if necessary)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P.1 (Title) and P.6 (last sentence of the Introduction)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	P.6
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P.6 (*"PROSPERO (CRD42021295352)"*)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P.1-2 (Title page)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P.15 and P.16 (section 4. and "*Contributions of authors' statement*")
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A (but the search algorithm is an update of Cortese et al. in Lancet Psychiatry 2018; see section 2.2.1. and supplementary material)
Support:			
Sources	5a	Indicate sources of financial or other support for the review	P. 16 ("*Role of funding source*")
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			

Rationale	6	Describe the rationale for the review in the context of what is already known	P. 5-6 (the entire Introduction)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P. 6 (last paragraph of the Introduction)
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P. 7-9 (sections 2.1.1. and 2.1.2. and 2.1.3. and 2.1.4.)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P. 9-10 (sections 2.2.1. and 2.2.2.)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P. 9-10 and supplementary material
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P. 11 (section 2.2.3.)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P. 11 (section 2.2.3.)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P. 11 (sections 2.2.3. and 2.3.)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P. 11 (section 2.3.
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P. 8 (section 2.1.3.)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P. 12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P. 12 (section 2.5.1.)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P.13-14 (section 2.5.2.)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P. 14 (assessment of the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons, NMA meta-regressions and subgroup analysis)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N /A

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P. 12-14 (section 2.4.)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P. 13 (*"The Confidence In Network Meta-Analysis (CINeMA) software will be used to assess the confidence of evidence contributing to each network estimate"*)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary Table 2. PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis.

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	P. 1 (Title) and P. 6 (last sentence of the Introduction)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	P. 3 P.3 P.3 N/A (protocol article) N/A (protocol article) P.3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	P. 5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P. 6 (last paragraph of the Introduction)

METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	P. 6 (registration in PROSPERO)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	P. 7-9 (sections 2.1.1. and 2.1.2. and 2.1.3. and 2.1.4.)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P. 9-10 (sections 2.2.1 and 2.2.2 + supplementary material)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P. 9-10 (and supplementary material)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P. 11 (section 2.2.3.)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P. 11-12 (sections 2.2.3. and 2.3.)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P. 11-12 (section 2.3.)
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	P. 13 (section 2.5.2.; only protocol article at this stage)
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P. 12 (section 2.4.)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in	P. 12-13 (sections 2.5.1 and 2.5.2.)

		means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	P. 13 (section 2.5.2.; only protocol article at this stage) N/A *"A common estimate for the heterogeneity variance will be assumed for all comparisons in the entire network, and we will assess the presence of statistical heterogeneity using the magnitude of the heterogeneity variance parameter (τ2) and total I^2 statistic."* N/A *"Incoherence between direct and indirect sources of evidence will be statistically assessed globally, by comparison of the fit and parsimony of consistency and inconsistency models [24], and locally, by calculation of the difference between direct and indirect estimates in all closed loops in the network [25]."*
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	P. 13-14 *("The Confidence In Network Meta-Analysis (CINeMA) software will be used to assess the confidence of evidence contributing to each network estimate [27]. This tool is based on a methodological framework which shows how much information each study contributes to the results from NMA by considering six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence."*)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P. 12-14 (section 2.4. + assessment of the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons, NMA meta-regressions and subgroup analysis)
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:	

		• Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	P. 14 (section 2.5.3.) P. 13 (*"To determine whether the results are affected by possible effect modifiers, we will conduct a network meta-regression for outcomes according to the following variables: study sponsorship, treatment duration, comorbid psychiatric disorders, study risk of bias, mean baseline severity, and percentage of participants treated with stable doses of medications in RCTs."*) N/A N/A
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	N/A (protocol article)
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	N/A (protocol article)
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	N/A (protocol article)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N/A (protocol article)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	N/A (protocol article)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches*	N/A (protocol article)

		may be needed to deal with information from larger networks.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	N/A (protocol article)
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	N/A (protocol article)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	N/A (protocol article)
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	N/A (protocol article)
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	N/A (protocol article)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	N/A (protocol article)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A (protocol article)

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	P. 14 (*"Role of funding source"*)

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

From: Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-784.

Appendix. Search syntax for each database (in alphabetical order).

A. BIOSIS Previews

TOPIC: (adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*) AND **TOPIC:** (Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera OR Viloxazine OR Qelbree OR Vivalan) AND **TOPIC:** (RCT OR ((clinical OR control*) NEAR/10 trial*) OR crossover OR "cross over" OR cross-over OR randomi* OR (random* NEAR/1 (allocat* OR assign* OR select*)) OR blind* OR placebo OR "control group") Indexes=BIOSIS Previews Timespan=All years

B. EMBASE

1. exp Attention Deficit Disorder with Hyperactivity/ or (adhd or hkd or addh or hyperkine* or "attention deficit*" or hyper-activ* or hyperactiv* or overactive or inattentive or impulsiv*).ti,ab.
2. exp Amphetamines/ or exp Bupropion/ or exp Clonidine/ or exp Methylphenidate/ or exp Dexmethylphenidate/ or exp Guanfacine/ or (Adderall or Amphetamine or Desoxyn* or Phenopromin or Amfetamine or Phenamine or Centramina or Fenamine or Levoamphetamine or Dexamfetamine or Dexamphetamine or Dexedrine or Dextroamphetamine or DextroStat or Oxydess or Methylamphetamine or Methylenedioxyamphetamine or Methamphetamine or Chloroamphetamine or Metamfetamine or Deoxyephedrine or Desoxyephedrine or Ecstasy or Atomoxetine or Biphentin or Bupropion or Amfebutamone or Zyntabac or Quomen or Wellbutrin or Zyban or Catapres* or Clonidine or Klofenil or Clofenil or Chlophazolin or Gemiton or Hemiton or Isoglaucon or Klofelin or Clopheline or Clofelin or Dixarit or Concerta or Daytrana or Methylphenidate or Equasym or Methylin or Tsentedrin or Centedrin or Phenidylate or Ritalin* or Duraclon or Elvanse or Focalin or Dexmethylphenidate or Guanfacine or Estulic or Tenex or Kapvay or Lisdexamfetamine or Vyvanse or Medikinet or Metadate or Modafinil or Nexiclon or Quillivant or Strattera OR Viloxazine OR Qelbree OR Vivalan).ti,ab.

3. (random$ or factorial$ or crossover$ or (cross over$) or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp. or crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
4. limit 3 to human

5. 1 and 2 and 4

C. ERIC

((SU.EXACT.EXPLODE("Attention Deficit Disorders") OR ti(adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*) OR ab(adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*)) AND (ti(Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera) OR ab(Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera OR Viloxazine OR Qelbree OR Vivalan))) AND (ti(RCT OR ((clinical OR control*) NEAR/10 trial*) OR crossover OR "cross over" OR cross-over OR randomi* OR (random* NEAR/1 (allocat* OR assign* OR select*)) OR blind* OR placebo OR "control group") OR ab(RCT OR ((clinical OR control*) NEAR/10 trial*) OR crossover OR "cross over" OR cross-over OR randomi* OR (random* NEAR/1 (allocat* OR assign* OR select*)) OR blind* OR placebo OR "control group"))

D. International Clinical Trials Registry Platform (WHO ICTRP)

(adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*) in Condition Field AND (Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera OR Viloxazine OR Qelbree OR Vivalan) in Intervention Field

E. MEDLINE

1. exp Attention Deficit Disorder with Hyperactivity/ or (adhd or hkd or addh or hyperkine* or "attention deficit*" or hyper-activ* or hyperactiv* or overactive or inattentive or impulsiv*).ti,ab.

2. exp Amphetamines/ or exp Bupropion/ or exp Clonidine/ or exp Methylphenidate/ or exp Dexmethylphenidate/ or exp Guanfacine/ or (Adderall or Amphetamine or Desoxyn* or Phenopromin or Amfetamine or Phenamine or Centramina or Fenamine or Levoamphetamine or Dexamfetamine or Dexamphetamine or Dexedrine or

Dextroamphetamine or DextroStat or Oxydess or Methylamphetamine or Methylenedioxyamphetamine or Methamphetamine or Chloroamphetamine or Metamfetamine or Deoxyephedrine or Desoxyephedrine or Ecstasy or Atomoxetine or Biphentin or Bupropion or Amfebutamone or Zyntabac or Quomen or Wellbutrin or Zyban or Catapres* or Clonidine or Klofenil or Clofenil or Chlophazolin or Gemiton or Hemiton or Isoglaucon or Klofelin or Clopheline or Clofelin or Dixarit or Concerta or Daytrana or Methylphenidate or Equasym or Methylin or Tsentedrin or Centedrin or Phenidylate or Ritalin* or Duraclon or Elvanse or Focalin or Dexmethylphenidate or Guanfacine or Estulic or Tenex or Kapvay or Lisdexamfetamine or Vyvanse or Medikinet or Metadate or Modafinil or Nexiclon or Quillivant or Strattera or Viloxazine or Qelbree or Vivalan).ti,ab.

3. (randomized controlled trial or controlled clinical trial).pt. or random$.ab. or placebo.ab. or drug therapy.fs. or trial.ab. or groups.ab.

4. exp animals/ not humans.sh.

5. 3 not 4

6. 1 and 2 and 5

F. ProQuest Dissertations & Theses: UK & Ireland and ProQuest Dissertations & Theses A&I

((ti(adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*) OR ab(adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*)) AND (ti(Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera) OR ab(Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera OR Viloxazine OR Qelbree OR Vivalan))) AND (ti(RCT OR ((clinical OR control*) NEAR/10 trial*) OR crossover OR "cross over" OR cross-over OR randomi* OR (random* NEAR/1 (allocat* OR assign* OR select*)) OR blind* OR placebo OR "control group") OR ab(RCT OR ((clinical OR control*) NEAR/10 trial*) OR crossover OR "cross over" OR cross-over OR randomi* OR (random* NEAR/1 (allocat* OR assign* OR select*)) OR blind* OR placebo OR "control group"))

G. PsycINFO

1. exp Attention Deficit Disorder with Hyperactivity/ or (adhd or hkd or addh or hyperkine* or "attention deficit*" or hyper-activ* or hyperactiv* or overactive or inattentive or impulsiv*).ti,ab.
2. exp Bupropion/ or exp Clonidine/ or exp Methylphenidate/ or (Adderall or Amphetamine or Desoxyn* or Phenopromin or Amfetamine or Phenamine or Centramina or Fenamine or Levoamphetamine or Dexamfetamine or Dexamphetamine or Dexedrine or Dextroamphetamine or DextroStat or Oxydess or Methylamphetamine or Methylenedioxyamphetamine or Methamphetamine or Chloroamphetamine or Metamfetamine or Deoxyephedrine or Desoxyephedrine or Ecstasy or Atomoxetine or Biphentin or Bupropion or Amfebutamone or Zyntabac or Quomen or Wellbutrin or Zyban or Catapres* or Clonidine or Klofenil or Clofenil or Chlophazolin or Gemiton or Hemiton or Isoglaucon or Klofelin or Clopheline or Clofelin or Dixarit or Concerta or Daytrana or Methylphenidate or Equasym or Methylin or Tsentedrin or Centedrin or Phenidylate or Ritalin* or Duraclon or Elvanse or Focalin or Dexmethylphenidate or Guanfacine or Estulic or Tenex or Kapvay or Lisdexamfetamine or Vyvanse or Medikinet or Metadate or Modafinil or Nexiclon or Quillivant or Strattera OR Viloxazine OR Qelbree OR Vivalan).ti,ab.

3. (double-blind or random* assigned or control).tw. 4. and/1-3
5. limit 4 to human

H. PubMed

("Attention Deficit Disorder with Hyperactivity"[Mesh] OR adhd[tiab] OR hkd[tiab] OR addh[tiab] OR hyperkine*[tiab] OR "attention deficit*"[tiab] OR hyper-activ*[tiab] OR hyperactiv*[tiab] OR overactive[tiab] OR inattentive[tiab] OR impulsiv*[tiab]) AND ("Amphetamines"[Mesh] OR "Bupropion"[Mesh] OR "Clonidine"[Mesh] OR "Methylphenidate"[Mesh] OR "Dexmethylphenidate"[Mesh] OR "Guanfacine"[Mesh] OR Adderall[tiab] OR Amphetamine[tiab] OR Desoxyn*[tiab] OR Phenopromin[tiab] OR Amfetamine[tiab] OR Phenamine[tiab] OR Centramina[tiab] OR Fenamine[tiab] OR Levoamphetamine[tiab] OR Dexamfetamine[tiab] OR Dexamphetamine[tiab] OR Dexedrine[tiab] OR Dextroamphetamine[tiab] OR DextroStat[tiab] OR Oxydess[tiab] OR Methylamphetamine[tiab] OR Methylenedioxyamphetamine[tiab] OR Methamphetamine[tiab] OR Chloroamphetamine[tiab] OR Metamfetamine[tiab] OR Deoxyephedrine[tiab] OR Desoxyephedrine[tiab] OR Ecstasy[tiab] OR Atomoxetine[tiab] OR Biphentin[tiab] OR Bupropion[tiab] OR Amfebutamone[tiab] OR Zyntabac[tiab] OR Quomen[tiab] OR Wellbutrin[tiab] OR Zyban[tiab] OR Catapres*[tiab] OR Clonidine[tiab] OR Klofenil[tiab] OR Clofenil[tiab] OR Chlophazolin[tiab] OR Gemiton[tiab] OR Hemiton[tiab] OR Isoglaucon[tiab] OR Klofelin[tiab] OR Clopheline[tiab] OR Clofelin[tiab] OR Dixarit[tiab] OR Concerta[tiab] OR Daytrana[tiab] OR Methylphenidate[tiab] OR Equasym[tiab] OR Methylin[tiab] OR Tsentedrin[tiab] OR Centedrin[tiab] OR Phenidylate[tiab] OR Ritalin*[tiab] OR Duraclon[tiab] OR Elvanse[tiab] OR Focalin[tiab] OR Dexmethylphenidate[tiab] OR Guanfacine[tiab] OR Estulic[tiab] OR Tenex[tiab] OR Kapvay[tiab] OR Lisdexamfetamine[tiab] OR Vyvanse[tiab] OR Medikinet[tiab] OR Metadate[tiab] OR Modafinil[tiab] OR Nexiclon[tiab] OR Quillivant[tiab] OR Strattera[tiab] OR Viloxazine[tiab] OR Qelbree[tiab] OR Vivalan[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])

I. SIGLE

(adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*) AND (Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR

Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera OR Viloxazine OR Qelbree OR Vivalan)

J. The Cochrane Library

#1 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees
#2 (adhd or hkd or addh or hyperkine* or "attention deficit*" or hyper-activ* or hyperactiv* or overactive or inattentive or impulsiv*):ti,ab
#3 MeSH descriptor: [Amphetamines] explode all trees
#4 MeSH descriptor: [Bupropion] explode all trees
#5 MeSH descriptor: [Clonidine] explode all trees
#6 MeSH descriptor: [Methylphenidate] explode all trees
#7 MeSH descriptor: [Dexmethylphenidate] explode all trees
#8 MeSH descriptor: [Guanfacine] explode all trees
#9 (Adderall or Amphetamine or Desoxyn* or Phenopromin or Amfetamine or Phenamine or Centramina or Fenamine or Levoamphetamine or Dexamfetamine or Dexamphetamine or Dexedrine or Dextroamphetamine or DextroStat or Oxydess or Methylamphetamine or Methylenedioxyamphetamine or Methamphetamine or Chloroamphetamine or Metamfetamine or Deoxyephedrine or Desoxyephedrine or Ecstasy or Atomoxetine or Biphentin or Bupropion or Amfebutamone or Zyntabac or Quomen or Wellbutrin or Zyban or Catapres* or Clonidine or Klofenil or Clofenil or Chlophazolin or Gemiton or Hemiton or Isoglaucon or Klofelin or Clopheline or Clofelin or Dixarit or Concerta or Daytrana or Methylphenidate or Equasym or Methylin or Tsentedrin or Centedrin or Phenidylate or Ritalin* or Duraclon or Elvanse or Focalin or Dexmethylphenidate or Guanfacine or Estulic or Tenex or Kapvay or Lisdexamfetamine or Vyvanse or Medikinet or Metadate or Modafinil or Nexiclon or Quillivant or Strattera or Viloxazine or Qelbree or Vivalan):ti,ab #10 #1 or #2

#11 #3 or #4 or #5 or #6 or #7 or #8 or #9 #12 #10 and #11

K. Web of Science

TOPIC: (adhd OR hkd OR addh OR hyperkine* OR "attention deficit*" OR hyper-activ* OR hyperactiv* OR overactive OR inattentive OR impulsiv*) AND **TOPIC:** (Adderall OR Amphetamine OR Desoxyn* OR Phenopromin OR Amfetamine OR Phenamine OR Centramina OR Fenamine OR Levoamphetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Oxydess OR Methylamphetamine OR Methylenedioxyamphetamine OR Methamphetamine OR Chloroamphetamine OR Metamfetamine OR Deoxyephedrine OR Desoxyephedrine OR Ecstasy OR Atomoxetine OR Biphentin OR Bupropion OR Amfebutamone OR Zyntabac OR Quomen OR Wellbutrin OR Zyban OR Catapres* OR Clonidine OR Klofenil OR Clofenil OR Chlophazolin OR Gemiton OR Hemiton OR Isoglaucon OR Klofelin OR Clopheline OR Clofelin OR Dixarit OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Tsentedrin OR Centedrin OR Phenidylate OR Ritalin* OR Duraclon OR Elvanse OR Focalin OR Dexmethylphenidate OR Guanfacine OR Estulic OR Tenex OR Kapvay OR Lisdexamfetamine OR Vyvanse OR Medikinet OR Metadate OR Modafinil OR Nexiclon OR Quillivant OR Strattera OR Viloxazine OR Qelbree OR Vivalan) AND **TOPIC:** (RCT OR ((clinical OR control*) NEAR/10 trial*) OR crossover OR "cross over" OR cross-over OR randomi* OR (random* NEAR/1 (allocat* OR assign* OR select*)) OR blind* OR placebo OR "control group") Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years