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Comparative efficacy and tolerability of pharmacological interventions for Attention-Deficit/Hyperactivity Disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis



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**Comparative efficacy and tolerability of pharmacological interventions 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: Attention-Deficit/Hyperactivity Disorder (ADHD) is a major public health issue. Pharmacological treatments play an important role in the multimodal treatment of ADHD. Currently, there is a lack of up-to-date and comprehensive evidence on how available ADHD drugs compare and rank in terms of efficacy and tolerability, in children/adolescents as well as in adults. We will conduct a network meta-analysis (NMA), integrating direct and indirect comparisons from randomised controlled trials (RCTs), to rank pharmacological treatments for ADHD according to their efficacy and tolerability profiles. **Methods and analysis:** We will search a broad range of electronic databases, including PubMed, MEDLINE, EMBASE, PsycINFO, ERIC, and Web of Science, with no date or language restrictions. We will also search for unpublished studies using international clinical trial registries and contacting relevant drug companies. We will identify and include available parallel-group, cross-over and cluster randomised trials that compare methylphenidate, dexamethylphenidate, amphetamine derivatives, lisdexamfetamine, atomoxetine, clonidine, guanfacine, bupropion, or modafinil (as oral therapy) either with each other or to placebo, in children, adolescents or adults with ADHD. Primary outcomes will be efficacy (indicated by reduction in severity of ADHD core symptoms measured on a standardised scale) and tolerability (the proportion of patients who left the study early due to side effects). Secondary outcomes will be global functioning, acceptability (proportion of patients who left the study early by any cause), and changes in blood pressure and body weight. NMA will be conducted in STATA within a frequentist framework. The quality of RCTs will be evaluated using the Cochrane risk of bias tool, and the quality of the evidence will be assessed using the GRADE approach. Subgroup and sensitivity analyses will be conducted to assess the robustness of the findings. **Ethics and dissemination:** No ethical issues are foreseen. The results will be presented at international meetings. **Registration:** PROSPERO CRD42014008976.

Strengths and limitations of the study

Strengths:

- This is the first comprehensive network meta-analysis addressing the efficacy and tolerability of medications for ADHD in children, adolescents and adults. By integrating direct and indirect evidence from all included studies, it will increase the precision of treatment estimates and allow for the ranking of available ADHD drugs in terms of both efficacy and acceptability;
- Subgroup and sensitivity analyses will address important clinical questions (e.g., differences between sexes, comparisons between children and adolescents, and subgroup analysis in participants without neurologic/psychiatric comorbidities);
- The findings of this network meta-analysis have the potential to inform and influence both clinical decision making and guideline development.

Limitations:

- As with any meta-analysis, the present one will be limited by the quality of the primary studies included in the systematic review. To properly address this issue, we will assess the quality of the studies included in the systematic review and the quality of the evidence using the Cochrane risk of bias tool and the GRADE approach, respectively, that are considered the gold standard for critical appraisal and quality of evidence.

BACKGROUND

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder ¹, characterised, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) ², by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. Hyperkinetic Disorder (HKD), as defined in the International Classification of Diseases, 10th Edition (ICD-10) ³, is a narrower diagnostic category, requiring both symptoms of inattention and hyperactivity/impulsivity, similarly to those individuals meeting criteria for the combined presentation of ADHD as per DSM-5 ². A large body of evidence shows that ADHD is frequently comorbid with other psychiatric conditions, the most common of which include oppositional defiant disorder, conduct disorder, specific learning disorders, mood and anxiety disorders, substance use disorders, sleep disturbances and other neurodevelopmental disorders such as autism spectrum disorder ^{4, 5}. The worldwide-pooled prevalence of ADHD is estimated at around 5% in school-age children ^{1, 6}. Impairing symptoms of ADHD persist into adulthood in around 65% of cases ⁷, with a pooled prevalence of adulthood ADHD around 2.5% ⁸. As a consequence of the nature of the core symptoms and the comorbid disorders, ADHD imposes a substantial burden on society in terms of psychological dysfunction, adverse educational and vocational outcomes, stress on families, and societal financial costs. Average annual incremental costs of ADHD have been estimated at \$143-\$266 billion in the U.S. ⁹ and are substantial in other countries as well (e.g., ^{10, 11}).

Available treatments for ADHD include pharmacological and non-pharmacological interventions. Pharmacological treatments are recommended as the first option in several guidelines/practice parameters (e.g., ¹²), at least for severe cases ^{13, 14}, or as a treatment strategy for patients who have not responded to non-pharmacological interventions ^{13, 14}. Medications for ADHD include psychostimulant (e.g., methylphenidate and amphetamine

derivatives) and non-psychostimulant drugs (e.g., atomoxetine, clonidine and guanfacine, among others). A large body of evidence from double-blind randomised controlled trials (RCTs), summarized in several meta-analyses in children, adolescents and/or adults, demonstrated that different classes of psychostimulants (e.g., methylphenidate¹⁵⁻¹⁸ or mixed amphetamine salts¹⁹ and other amphetamine derivatives²⁰) and some non-psychostimulant treatments, such as atomoxetine²¹⁻²⁴, are significantly more efficacious than placebo, at least in the short term, when considering ADHD core symptoms as main outcome. However, two recent Cochrane reviews^{25, 26} have questioned the quality of the evidence from the available RCTs, in contrast with a previous review by the National Institute for Health and Care Excellence (NICE)¹³, that assessed the quality of the evidence as *high*. Whereas previous meta-analyses focused on the efficacy/tolerability of ADHD drugs versus placebo/control, there is currently no published meta-analytic evidence that can provide a framework to establish a hierarchy of the efficacy and acceptability/tolerability among the available pharmacological treatments for ADHD, in children as well as in adults. Such evidence would be invaluable in day-to-day clinical practice, where clinicians are faced with selecting specific medications for the treatment of ADHD. Furthermore, given the current debate around the appropriateness of behavioural interventions vs. medications as first line treatment for ADHD²⁷, the uncertainty on the efficacy/effectiveness of non-pharmacological treatments for ADHD core symptoms^{27, 28}, and the increasing trend in the prescription of ADHD medications in some countries^{27, 29, 30}, an up-to-date and accurate estimate of the efficacy, tolerability and safety of the most common ADHD drugs is paramount from a public health standpoint.

Network Meta-Analysis (NMA) is a statistical method of synthesizing information from a network of trials that have addressed the same question using different interventions³¹. A NMA relies on the combination of direct and indirect evidence, which can increase

precision while randomization is preserved³²⁻³⁶. Therefore, compared to standard pairwise meta-analyses, NMA gives a higher degree of precision in the estimation of efficacy and acceptability/tolerability of drugs. A further application of the NMA methodology is the possibility of ranking the interventions included in the network according to their relative efficacy and safety, which in itself is highly relevant for treatment decision making in the daily clinical practice.

Objectives

To rank pharmacological treatments in patients with ADHD, in terms of:

- 1. Overall efficacy on ADHD core symptoms;
- 2. Tolerability;
- 3. Global functioning;
- 4. Acceptability;
- 5. Changes in blood pressure and weight.

METHODS

Methods for this systematic review have been developed according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions³⁷. This systematic review and NMA is registered in the PROSPERO database (registration number: CRD42014008976).

Types of participants

Inclusion criteria

Studies that include children (≥ 5 and < 12 years), adolescents (≥ 12 and < 18 years) and/or adults (≥ 18 years), either in- or outpatients, who: 1) meet DSM-III, III-R, IV, IV-TR

or 5 criteria for a primary diagnosis of ADHD or ICD-10 criteria for a primary diagnosis of HKD (we will not include studies using DSM-II criteria since they did not use standardised criteria). There will be no restriction on ADHD subtype/presentation, gender, IQ or socio-economic status of participants. As for comorbidities, we will include studies in which some, or all, participants have one or more psychiatric or neurological comorbidities (except rare comorbidities, e.g., rare genetic syndromes), unless participants were pharmacologically treated during the study for these comorbidities (e.g., antiepileptic drugs for epilepsy or mood stabilizers for bipolar disorders).

Exclusion criteria

We will exclude: 1) studies recruiting patients with a diagnosis of Minimal Brain Dysfunction, which would not be comparable with DSM definitions of ADHD or ICD definitions of HKD; 2) trials in which ADHD is a comorbid disorder secondary to another rare medical or (neuro)psychiatric diagnosis (e.g., fragile X or foetal alcohol syndrome); 3) studies enrolling subjects defined as “hyperkinetic” or “hyperactive” without application of standardised diagnostic criteria; (4) studies recruiting patients who were taking ADHD medication prior to entering the study, unless participants completed an appropriate wash out period before starting the study trial (see Table 1 for the details about recommended wash out periods for each individual drug); (5) studies including (a) subjects who previously responded (according to the definition provided in the study) to the same medication tested in the randomised phase (irrespective of washout period) or (b) subjects who were responders or stabilized/optimized to an ADHD medication (where stabilized/optimized means responders) during a run-in/open label phase before randomisation (irrespective of wash out period); (6) studies in which all included subjects were deemed to be “resistant” to a previous ADHD drug, as this would violate the transitivity assumption of NMA³¹.

Types of interventions

We will include studies assessing any of the following drugs, as oral monotherapy (tablets, capsules, chewable compounds or liquid formulations), compared to each other or with placebo: methylphenidate, dexamethylphenidate, atomoxetine, amphetamine derivatives, lisdexamfetamine, clonidine, guanfacine, bupropion, and modafinil. Only studies where medications were given within the licensed or recommended dose level (see Tables 2 and 3), will be included. Both fixed-dose and flexible-dose designs will be allowed. Studies assessing the efficacy of multimodal treatments including the combination of ADHD drug(s) plus psychotherapy (for ADHD or other disorders/conditions) will be excluded. However, studies in which ADHD drugs of interest for the present meta-analysis are combined with psychoeducation only, rather than psychotherapy, will be retained. Study arms with medication only as monotherapy will be included from these studies if compared with another medication only or placebo from the same study. Studies comparing any ADHD drug to treatment as usual or assessing the efficacy of additional drugs in participants resistant to the first ADHD drug will not be included. Studies using a single dose of drug will also be excluded. In terms of minimum duration of the pharmacological treatment, while previous meta-analyses have included studies with treatment duration of 1 day (e.g., ²⁵) and other meta-analyses have excluded studies lasting less than 3 weeks (e.g., ³⁸), we will include trials with treatment duration of at least 7 consecutive days, since response to adequate doses of psychostimulants can be appreciated already after approximately 1 week of treatment and, to our knowledge, there is no clear evidence that placebo effects change over time in studies of ADHD drugs.

Timing of outcome assessment

We will include studies assessing efficacy of drugs both in the short term (outcomes up to 12 weeks) and in the medium term (up to 26 weeks). For short term studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 12 weeks. For medium term studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 26 weeks. We will consider also longer term outcomes (at least 52 weeks). For these studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 52 weeks.

Types of studies

Inclusion criteria

Only double-blinded RCTs will be included. Three types of trials will be eligible for inclusion: parallel-group RCTs, crossover trials and cluster trials. For cross-over studies, to address concerns around possible “carry over” effects³⁹, we will use data from the pre-crossover phase, whenever this is reported in the paper. When data for the pre-cross over phase are not reported, we will contact study authors to gather them. If pre-crossover data are not reported and not available upon request, we will use data at the endpoint (after crossing over), derived from appropriate statistical methods (i.e., paired t-test)⁴⁰, only if there was a washout period (see Table 1) between the two phases (pre and post crossover) of the trial. As for cluster trials, according to the Cochrane Handbook, they can be combined with individually randomised RCTs⁴¹. In this case, approximately correct analyses will be performed by dividing the binary data (the number of participants and the number experiencing the event) as presented in a report by a ‘design effect’⁴¹. This is calculated by using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) (Design effect = $1 + (m - 1) * ICC$)⁴¹. If the ICC is not reported, it will be

assumed to be 0.1⁴². For continuous data only, the sample size will be reduced; means and standard deviations will remain unchanged. Data from the withdrawal phase of a trial, in which already treated subjects are randomised to either continue medication or switch to placebo, following an open label phase, will be used only if subjects were not stabilized during the open label phase or if there was a washout period before randomisation to the continuation phase.

Exclusion criteria

Quasi-randomised controlled trials, in which treatment assignment is decided through methods such as alternate days of the week, or studies using Latin square approach without adequate randomisation, will be excluded. We will also exclude open-label or single blind RCTs, long-term studies using a maintenance design, and N-of-1 trials.

Types of outcome measures

Primary outcomes

- Efficacy (as continuous outcome) on severity of ADHD core symptoms (total combined, i.e. inattentive plus hyperactive/impulsive symptoms), measured as endpoint score on a standardised scale filled out by parents, teachers, patients or clinician(s). Where there are ratings based on two or more scales, only one scale will be selected among the following ones, in the following order of preference: ADHD Rating Scale (*total score*), SNAP ADHD (*total score*), Conners rating scale (any version, *ADHD total score*), or other ADHD scales. Total scores for ADHD symptoms will be selected and evaluated. However, when total scores are not available and only sub-scales of ADHD measures (i.e., measuring the dimensions of inattention and hyperactivity/impulsivity symptoms of ADHD separately) are

reported, the effect size for each of these will be calculated separately and aggregated to estimate the overall effect. When endpoint scores are not reported but change scores are, we will use the latter scores⁴³. We will conduct separate analyses for measures rated by 1) clinicians, 2) parents, 3) teachers, and 4) patients (self). Teachers and clinicians' scores will be considered for the primary analysis of studies in children/adolescents and adults, respectively.

- Tolerability of treatment, defined as the proportion of patients who left the study early due to any side effects during the first 12 weeks of treatment.

Secondary outcomes

- Global functioning, measured by the Clinical Global Impressions-Improvement (CGI-I, investigator's rating) considered at time-points closest to 12 weeks, and, if available, at 26 and 52 weeks. We will consider the proportion of participants who improved at endpoint based on the final CGI-I score of 1-2;
- Acceptability of treatment, defined as the proportion of patients who left the study early for any reason during the first 12 weeks of treatment;
- Change in blood pressure (diastolic and systolic), measured in mmHg;
- Change in body weight, measured in Kg.

Search strategy

We will search for both published and unpublished RCTs meeting the inclusion criteria.

Electronic searches

Electronic literature search will be conducted by two members of the Cochrane Schizophrenia Group (FS and JX) with input from the EAGG members. The following search

resources will be considered: PubMed, MEDLINE, EMBASE, PsycINFO, ERIC and Web of Science (including Science Citation Index Expanded (SCI-EXPANDED), Social Science Citation Index (SSCI), Conference Proceedings Citation Index- Science (CPCI-S), and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)) via Web of Knowledge. We will also search the following international databases:

1. WHO International Clinical Trials Registry Platform (ICTRP), including:
 - *Australian New Zealand Clinical Trials Registry (ANZCTR) (including clinical trials from Therapeutic Goods Administration (TGA))*
 - *Brazilian Clinical Trials Registry (ReBec)*
 - *Chinese Clinical Trial Register (ChiCTR)*
 - *Clinical Research Information Service (CRiS), Republic of Korea*
 - *ClinicalTrials.gov (including clinical trials from FDA)*
 - *Clinical Trials Registry - India (CTRI)*
 - *Cuban Public Registry of Clinical Trials (RPCEC)*
 - *EU Clinical Trials Register (EU-CTR) (including clinical trials from the European Medicines Agency (EMA))*
 - *German Clinical Trials Register (DRKS)*
 - *Iranian Registry of Clinical Trials (IRCT)*
 - *ISRCTN.org (including clinical trials from controlled-trials.com, The Wellcome Trust (UK), UK trials (UK), Action Medical Research (UK), the Medicines and Healthcare products Regulatory Agency (MHRA), and National Research Register)*
 - *Japan Primary Registries Network (JPRN) (including clinical trials from UMIN-CTR, JapicCTI, and JMACCT)*
 - *Pan African Clinical Trial Registry (PACTR)*
 - *Sri Lanka Clinical Trials Registry (SLCTR)*

- *The Netherlands National Trial Register (NTR)*
- *Thai Clinical Trials Register (TCTR)*
2. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
3. UK Clinical Trials Gateway
4. BIOSIS Previews via Web of Knowledge
5. SEAGLE (OpenGrey)
6. ProQuest Theses and Dissertations
7. ClinicalTrials.gov
8. <http://www.fda.gov/>
9. www.ema.europa.eu

The following search terms will be used for 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]) AND (randomised controlled trial[pt] OR controlled
clinical trial[pt] OR randomised[tiab] OR placebo[tiab] OR clinical trials as
topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])

Search terms and syntax will be adapted as required for each of the databases.

Reference lists and other sources

The references of all selected studies will be searched for other published reports and citations of unpublished studies. Relevant review papers will be checked. In addition, websites of the most relevant pharmaceutical companies manufacturing ADHD drugs will be hand-searched for published, unpublished and ongoing controlled trials. Companies producing ADHD drugs will also be contacted to inquire about any additional relevant study. New trials which have been completed will be included if usable data are provided by the pharmaceutical company.

Identification and selection of studies

Studies identified through electronic and manual searches will be listed with citation, titles and abstracts, in Endnote; duplicates will be excluded using the Endnote function “remove duplicates”. The eligibility for inclusion process will be conducted in two separate stages:

1. Two authors will independently screen title and abstracts of all non-duplicated papers 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, a third senior author will act as arbitrator. If any doubt about inclusion exists, the article will proceed to the next stage;
2. The full-text version of the articles passing stage 1 screening will be downloaded and assessed for eligibility by two authors, independently. Discrepancies will be resolved by consensus between the two authors and, if needed, a third senior author 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.

Data extraction

The following data will be collected from each included study:

- Study citation, year(s) of study, year of publication, location, setting, number of centres, design (type of RCT), sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Characteristics of study participants, including: gender distribution, mean and range of age, presence and type of co-morbid (neuro)psychiatric conditions, mean (and SD) IQ, number randomised into each group, number of dropouts, and whether ADHD medications naïve at baseline or previously exposed to other ADHD medications;

- Characteristics of interventions including mean and maximum doses, formulation, add-on interventions (if any), and whether forced dose or optimised treatment;
- Time(s) of outcome measurement;
- Outcome measures reported including whether the data are based on an intention-to-treat (ITT) or completers only sample. For ITT samples, methods of imputation will be noted.

One reviewer will input outcome data into Excel. This will be independently cross-checked by another reviewer. Data from studies included in previous systematic reviews only will be extracted by one reviewer and independently cross-checked by a second reviewer for accuracy. Degree of agreement between the independent raters will be reported in terms of kappa coefficients and percentage agreements for main outcomes, study and population characteristics and risk of bias items (see below).

Risk of bias assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool, as a reference ⁴¹. The following five domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome: was knowledge of the allocated treatment adequately prevented during the study?
4. Incomplete outcome data for the primary outcomes: were incomplete outcome data adequately addressed?
5. Selective outcome reporting: are reports of the study free from suggestion of selective outcome reporting?

A description of what was reported to have happened in each study will be provided, and a judgment on the risk of bias will be made for each domain, based on the following three categories: “high risk of bias”, “low risk of bias” and “unclear risk of bias”. The potential bias for “sponsorship bias” will be assessed as a separate item. As in Catala-Lopez et al.³⁸, the overall rating of risk of bias for each study will be the lowest rating for any of the criteria (e.g., if any domain is scored high risk of bias, the study will be considered high risk of bias). Two independent review authors will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreement will be resolved through discussion and in consultation with the senior authors. Where necessary, the authors of the studies will be contacted for further information.

Measures of treatment effect

Relative treatment effects

Continuous outcomes: where different measures are used to assess the same outcome, data will be pooled with standardized mean difference (SMD) Hedges’s adjusted g ⁴¹. Dichotomous outcomes will be analysed by calculating the odds ratio (OR). Results from the NMA will be presented as summary relative effect sizes (SMD or OR) and relative 95% confidence intervals for each possible pair of treatments.

Relative treatment ranking

We will estimate the probability for each intervention to be the best for each outcome, given the relative effect sizes as estimated in NMA. As described in Salanti⁴⁴, we will obtain a hierarchy of the competing interventions using the Surface Under the Cumulative Ranking curve (SUCRA) and mean ranks. SUCRA values will be expressed as percentage, showing the relative probability of an intervention to be among the best options without uncertainty.

Dealing with missing data

Missing dichotomous outcome data will be managed according to the ITT principle, and it will be assumed that patients in the full analysis set who dropped out after randomization 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 by the trial authors; if LOCF (or other imputation method) data are not available, missing data will be analysed using a validated method. We will use published SD, where available. If SD are not available from the publication, SD will be calculated from p-values, t-values, confidence intervals or standard errors⁴⁵. If these values are missing, attempts will be made to obtain SD or p-values, t-values, confidence intervals or standard errors from trial authors. Where SDs are not available, a validated method for imputation will be used⁴⁶. We will check that the original SDs are normally distributed, so that the imputed SD represents the average. Where imputation is employed, data will be interpreted with caution, and the degree of heterogeneity observed will need to be taken into account when interpreting findings. A sensitivity analysis will also be undertaken to examine the effect of imputation of the findings.

Assessment of clinical and methodological heterogeneity within treatment comparisons

The studies synthesized in each pairwise comparison need to be similar enough in terms of patient characteristics, setting, and outcome definitions, among others, in order to obtain interpretable and useful results⁴¹. To evaluate the degree of clinical and methodological heterogeneity, we will generate descriptive statistics for trial and study population characteristics across all eligible trials. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics⁴¹.

Assessment of transitivity across treatment comparisons

The assumption of transitivity underlies NMA and needs careful evaluation. In the case that transitivity is not plausible in a network of trials, the indirect and mixed treatment effect estimates are not valid. To infer about the assumption of transitivity⁴⁷:

1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs;
2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons. If the distributions are balanced across comparisons, we will conclude against evidence of intransitivity⁴⁸.

Data analysis

Synthesis of results

First, pairwise meta-analyses will be conducted for all outcomes and comparisons at each time point, using a random-effects model⁴⁹. Then, a NMA will be performed within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons and accounting for correlations induced by multi-arm studies^{47, 50}. Both pairwise meta-analysis and NMA will be performed for children/adolescents and adults, respectively. The analysis will be performed using STATA v.13. (MRC Biostatistics Unit, Cambridge, UK, <http://cmimg.cochrane.org/network-meta-analysis-toolkit>); the codes and description of the methodology can be found in <http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis>⁵¹⁻⁵³. Studies in children and adolescents will be combined in the statistical analyses. For primary outcomes, we will also assess the quality of evidence using GRADE⁵⁴ (GRADE Working Group 2004).⁵⁴ The criteria considered are: study limitations, indirectness, inconsistency, imprecision, and reporting bias. We will assign four levels of quality of evidence: *high, moderate, low, and very low*.

Assessment of statistical heterogeneity

In standard pairwise meta-analyses, we will estimate different heterogeneity variances for each pairwise comparison. In network meta-analysis, we will assume a common estimate for the heterogeneity variance (τ^2) within and across comparisons. The presence of statistical heterogeneity within each pairwise comparison will be assessed by visual inspection of the forest plots and by calculating the I-squared statistic and its confidence limits⁵⁵. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the common τ^2 estimated from the NMA models⁵⁶. For dichotomous outcomes, the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner et al.⁵⁷.

Assessment of statistical incoherence

Local and global approaches will be used to evaluate statistical incoherence. To evaluate the presence of incoherence locally, we will use the loop-specific approach⁵⁸. This method evaluates the incoherence assumption by calculating the incoherence factor as the difference between direct and indirect estimates for a specific comparison in each closed loop formed by the network of trials (using the Bucher method) and their relative 95% confidence intervals. The incoherence factor is the logarithm of the ratio of two risk ratios (RRR) from direct and indirect evidence in the loop. Then we will examine whether there are any material discrepancies; if the 95% CI does overlap with 1, the hypothesis of incoherence is not rejected, as described in Salanti⁵⁹. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using the ‘ifplot’ command in STATA. To check the assumption of consistency in the entire network, we will use the ‘design-by-treatment’ model⁶⁰. This method accounts for different source of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm

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2
3 trials) give different results as well as disagreement between direct and indirect evidence.
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5 Using this approach we will infer the presence of inconsistency from any source in the entire
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7 network based on a chi-square test. The design-by-treatment model will be performed in
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9 STATA using the 'mvmeta' command. Inconsistency and heterogeneity are interweaved; to
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11 distinguish between these two sources of variability we will employ the I-squared for
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13 inconsistency that measures the percentage of variability that cannot be attributed to random
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15 error or heterogeneity (within comparison variability) ⁵⁶.
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20 21 *Investigation of heterogeneity and inconsistency*

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23 In the case of important clinical or statistical inconsistency, the feasibility of multiple-
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25 treatments meta-regression or subgroup analysis will be considered to investigate the possible
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27 sources of heterogeneity and incoherence by using the following effect modifiers (for primary
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29 outcomes only):
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- 31 1. studies sponsored vs. those not sponsored by pharmaceutical companies;
- 32 2. males vs. females;
- 33 3. children vs. adolescents, since some medications (e.g., SSRIs) have been reported to
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35 have different efficacy in children vs. adolescents ⁵⁹;
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43 *Sensitivity analyses*

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45 We will explore the feasibility of conducting the following sensitivity analyses by
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47 excluding:
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- 49 1) studies where all participants have IQ < 70;
- 50 2) studies where all participants have psychiatric/neurologic comorbidities;
- 51 3) studies lasting less than 2 weeks;
- 52 4) studies for which imputation of missing data was required;
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- 5) studies with overall high or unclear risk of bias;
 - 6) cross-over trials;
 - 7) studies including patients resistant to ADHD medication;
 - 8) studies recruiting only non-treatment-naïve patients;
- 7) A final sensitivity analysis will address whether unbalanced doses affected the results. To exclude trials with non-equivalent comparisons, we will apply a previously validated approach used for antidepressant trials.⁶⁰ For this, we put together a roster (see Tables 2-3) in which low and high doses of the drugs included in the present NMA are described. Tables 2-3 are based on FDA indications whenever possible. This roster will be employed to detect inequalities in dosing that could affect comparative efficacy by excluding trials with low doses of one drug and high doses of the other (or vice-versa). We will not consider starting doses if these were supposed to be increased during the trial.

ETHICS AND DISSEMINATION

No ethical issues are foreseen since ethical approval has been obtained for each study that will be included in the systematic review/meta-analysis. The results of this study will be published in a peer-reviewed journal and will be also possibly presented at national and international meetings of (child) psychiatry, psychology, and paediatrics.

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GUARANTOR OF THE REVIEW: Dr. Samuele Cortese

AUTHORS' CONTRIBUTION: Dr. Cortese drafted the protocol (with the exception of the literature search and statistical analysis sections). Drs. Shokraneh and Xia drafted the literature search section. Dr. Del Giovane drafted the statistical analysis section. All other co-authors critically reviewed and amended the initial draft of the protocol.

COMPETING INTEREST STATEMENT

Dr. Cortese has received reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non profit organization, in relation to lectures that he delivered for ACAMH.

Dr. Adamo has received travel support from Shire to attend a meeting in 2015

Dr. Mohr-Jensen has been a speaker for HB Pharma/Medice.

Dr. Carucci collaborated within projects from the European Union (7FP) and has received travel support from Shire Pharmaceutical Company; she collaborated as sub-investigator in sponsored clinical trial by Shire Pharmaceutical Company.

Dr. Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, Otsuka, PCM scientific, Shire and Viforpharma. He received conference support or speaker's fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press.

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Dr. Steinhausen has worked as an advisor and speaker for the following pharmaceutical companies: Janssen-Cilag, Eli Lilly, Novartis, Medice, Shire, and UCB and has also received

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Dr. Cipriani has served as an expert witness for a patent litigation case about quetiapine extended-release and is supported by the NIHR Oxford Cognitive Health Clinical Research Facility.

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Drs. Hayes, Bhatti, Del Giovane, Atkinson, Simonoff, Barbui, Purgato, Shokraneh and Xia report no competing conflicts of interest.

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Table 1. Washout periods.

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

Table 2. Dose range of medications included in the network meta-analysis for children/adolescents, according to the FDA whenever possible (as retrieved in <https://dailymed.nlm.nih.gov/dailymed/> or <http://www.accessdata.fda.gov/>; other source: Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attentiondeficit/hyperactivity disorder: emerging concepts from new data. J Child Adolesc Psychopharmacol 2007;17:393-406)

Drug	Min. daily dose	Max. daily dose
Methylphenidate hydrochloride immediate release	10 mg	60 mg
Methylphenidate hydrochloride intermediate acting	20 mg	60 mg
Methylphenidate hydrochloride long acting	18 mg	54 mg (children) 72 mg (adolescents) (do not exceed 2 mg/Kg/day)
Methylphenidate hydrochloride oral solution	10 mg	60 mg
Methylphenidate hydrochloride chewable tablets	10 mg	60 mg
d,l-threo Methylphenidate slow release	20 mg	60 mg
Dexmethylphenidate (d-threo-methylphenidate) immediate release	5 mg	20 mg
Dexmethylphenidate (d-threo-methylphenidate) XR	5 mg (children)	20 mg
Dextro-amphetamine immediate release	2.5 mg (children 3-5 y) 5 mg (children \geq 6 y)	Children 3-5 y: not specified Children \geq 6 y: 40 mg
Dextro-amphetamine ER	10 mg (children 6-12 y and adolescents 13-17 y)	30 mg (children 6-12 y) Adolescents: not specified
Mixed Amphetamine Salts	2.5 mg (children 3-5 y) 5 mg (children \geq 6 y)	40 mg (children \geq 6 y)
Mixed Amphetamine Salts XR	10 mg (children \geq 6 y) 10 mg, increased to 20 mg (adolescents 13-17 y)	30 mg (children \geq 6 y) Adolescents 13-17 y and
Lisdexamfetamine	30 mg (individuals \geq 6 y)	70 mg (individuals \geq 6 y)
Atomoxetine	0.5 mg/Kg (children and adolescents \leq 70 Kg) 40 mg (children and adolescents $>$ 70 Kg and adults)	1.4 (1.8 in Europe) mg/Kg or 100 mg, whichever less (children and adolescents \leq 70 Kg) 100 mg (children and adolescents $>$ 70 Kg)
Clonidine immediate release	Children/adolescents $<$ 45 Kg: 0.05 mg	Children/adolescents $<$ 45 Kg: 0.2 mg

	Children/adolescents > 45 Kg: 0.1 mg	Children/adolescents > 45 Kg: 0.4 mg
Clonidine extended release	0.1 mg	0.4 mg
Guanfacine immediate release	0.5 mg	N/S
Guanfacine extended release	1 mg	7 mg
Bupropion IR	N/S	N/S
Bupropion SR	N/S	N/S
Bupropion XL	N/S	N/S
Modafinil	200 mg	400 mg

Table 3. Dose range of medications included in the network meta-analysis for adults, according to the FDA whenever possible (as retrieved in <https://dailymed.nlm.nih.gov/dailymed/> or <http://www.accessdata.fda.gov/>; other sources: <http://integratedcare-nw.org/docs/PCPtraining/AdultADHDSummary-Recommendations.pdf>; Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attention deficit/hyperactivity disorder: emerging concepts from new data. *J Child Adolesc Psychopharmacol* 2007;17:393-406)

Drug	Min. daily dose	Max. daily dose
Methylphenidate hydrochloride immediate release	10 mg	60 mg
Methylphenidate hydrochloride intermediate acting	20 mg	60 mg
Methylphenidate hydrochloride long acting	18-36 mg	72 mg
Methylphenidate hydrochloride oral solution	10 mg	60 mg
Methylphenidate hydrochloride chewable tablets	10 mg	60 mg
d,l-threo Methylphenidate slow release	20 mg	60 mg
Dexmethylphenidate (d-threo-methylphenidate) immediate release	5 mg	20 mg
Dexmethylphenidate (d-threo-methylphenidate) XR	10 mg (adult)	20 mg
Dextro-amphetamine immediate release	N/S	N/S
Dextro-amphetamine ER	20 mg	N/S
Mixed Amphetamine Salts	N/S	N/S
Mixed Amphetamine Salts XR	20 mg	N/S
Lisdexamfetamine	30 mg	70 mg
Atomoxetine	N/S	100 mg
Clonidine immediate release	N/S	N/S
Clonidine extended release	0.1 mg	0.4 mg
Guanfacine immediate release	0.5 mg	N/S
Guanfacine extended release	1 mg	7 mg
Bupropion IR	100 mg bid	100 mg tid

Bupropion SR	150 mg qam	150 mg bid
Bupropion XL	150 mg qam	300 mg qam
Modafinil	200 mg	400 mg

For peer review only

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review: Pag. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Pag. 5 and 8
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Pag. 1-3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review. Pag. 24
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review Pag. 24
Sponsor	5b	Provide name for the review funder and/or sponsor Pag. 24
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Pag. 24
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Pag.6-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Pag. 8
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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 Pag.8-13
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 Pag. 13-17
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 Pag. 15
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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) Pag. 16-17
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 Pag. 17-18
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 Pag. 17-18
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Pag. 12-13
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 Pag. 18-19
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Pag. 21
	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) Pag. 21-23
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	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) Pag. 23
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*** 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.**

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Comparative efficacy and tolerability of pharmacological interventions for Attention-Deficit/Hyperactivity Disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis



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Primary Subject Heading:	Mental health

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Secondary Subject Heading:	Mental health
Keywords:	Attention-Deficit/Hyperactivity Disorder, pharmacological treatment, acute treatment, systematic review, network meta-analysis

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**Comparative efficacy and tolerability of pharmacological interventions 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: Attention-Deficit/Hyperactivity Disorder (ADHD) is a major public health issue. Pharmacological treatments play an important role in the multimodal treatment of ADHD. Currently, there is a lack of up-to-date and comprehensive evidence on how available ADHD drugs compare and rank in terms of efficacy and tolerability, in children or adolescents as well as in adults. We will conduct a network meta-analysis (NMA), integrating direct and indirect comparisons from randomised controlled trials (RCTs), to rank pharmacological treatments for ADHD according to their efficacy and tolerability profiles.

Methods and analysis: We will search a broad range of electronic databases, including PubMed, MEDLINE, EMBASE, PsycINFO, ERIC, and Web of Science, with no date or language restrictions. We will also search for unpublished studies using international clinical trial registries and contacting relevant drug companies. We will identify and include available parallel-group, cross-over and cluster randomised trials that compare methylphenidate, dexamethylphenidate, amphetamine derivatives, lisdexamfetamine, atomoxetine, clonidine, guanfacine, bupropion, or modafinil (as oral therapy) either with each other or to placebo, in children, adolescents or adults with ADHD. Primary outcomes will be efficacy (indicated by reduction in severity of ADHD core symptoms measured on a standardised scale) and tolerability (the proportion of patients who left a study early due to side effects). Secondary outcomes will be global functioning, acceptability (proportion of patients who left the study early by any cause), and changes in blood pressure and body weight. NMA will be conducted in STATA within a frequentist framework. The quality of RCTs will be evaluated using the Cochrane risk of bias tool, and the quality of the evidence will be assessed using the GRADE approach. Subgroup and sensitivity analyses will be conducted to assess the robustness of the findings. **Ethics and dissemination:** No ethical issues are foreseen. Results from this study will be published in a peer-reviewed journal and possibly presented at relevant national and

international conferences. **Registration:** PROSPERO-National Institute of Health Research (NIHR) Prospective Register of Systematic Reviews (CRD42014008976).

Strengths and limitations of the study

Strengths:

- This is the first comprehensive network meta-analysis addressing the efficacy and tolerability of medications for ADHD in children, adolescents and adults. By integrating direct and indirect evidence from all included studies, it will increase the precision of treatment estimates and allow for the ranking of available ADHD drugs in terms of both efficacy and acceptability;
- Subgroup and sensitivity analyses will address important clinical questions (e.g., differences between sexes comparisons between children and adolescents, and subgroup analysis in participants without neurologic/psychiatric comorbidities);
- The findings of this network meta-analysis have the potential to inform and influence both clinical decision making and guideline development.

Limitations:

- As with any meta-analysis, the present one will be limited by the quality of the primary studies included in the systematic review. To properly address this issue, we will assess the quality of the studies included in the systematic review and the quality of the evidence using the Cochrane risk of bias tool and the GRADE approach, respectively, that are considered the gold standard for critical appraisal and quality of evidence.

BACKGROUND

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder ¹, characterised, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) ², by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. Hyperkinetic Disorder (HKD), as defined in the International Classification of Diseases, 10th Edition (ICD-10) ³, is a narrower diagnostic category, requiring both symptoms of inattention and hyperactivity/impulsivity, similarly to those individuals meeting criteria for the combined presentation of ADHD as per DSM-5 ². A large body of evidence shows that ADHD is frequently comorbid with other psychiatric conditions, the most common of which include oppositional defiant disorder, conduct disorder, specific learning disorders, mood and anxiety disorders, substance use disorders, sleep disturbances and other neurodevelopmental disorders such as autism spectrum disorder ^{4, 5}. The worldwide-pooled prevalence of ADHD is estimated at around 5% in school-age children ^{1, 6}, albeit with a substantial heterogeneity between studies, accounted for by differences in either the method of assessment or the diagnostic criteria employed. Impairing symptoms of ADHD persist into adulthood in around 65% of cases ⁷, with a pooled prevalence of adulthood ADHD around 2.5% ⁸. As a consequence of the nature of the core symptoms and the comorbid disorders, ADHD imposes a substantial burden on society in terms of psychological dysfunction, adverse educational and vocational outcomes, stress on families, and societal financial costs. Average annual incremental costs of ADHD have been estimated at \$143-\$266 billion in the U.S. ⁹ and are substantial in other countries as well (e.g., ^{10, 11}).

Available treatments for ADHD include pharmacological and non-pharmacological interventions. Pharmacological treatments are recommended as the first option in several guidelines/practice parameters (e.g., ¹²), at least for severe cases ^{13, 14}, or as a treatment strategy for patients who have not responded to non-pharmacological interventions ^{13, 14}.

Medications for ADHD include psychostimulant (e.g., methylphenidate and amphetamine derivatives) and non-psychostimulant drugs (e.g., atomoxetine, clonidine and guanfacine, among others). A large body of evidence from double-blind randomized controlled trials (RCTs), summarized in several meta-analyses in children, adolescents and/or adults, demonstrated that different classes of psychostimulants (e.g., methylphenidate¹⁵⁻¹⁸ or mixed amphetamine salts¹⁹ and other amphetamine derivatives²⁰) and some non-psychostimulant treatments, such as atomoxetine²¹⁻²⁴, are significantly more efficacious than placebo, at least in the short term, when considering ADHD core symptoms as main outcome. However, two recent Cochrane reviews^{25, 26} have questioned the quality of the evidence from the available RCTs, in contrast with a previous review by the National Institute for Health and Care Excellence (NICE)¹³, that assessed the quality of the evidence as *high*.

Importantly, previous systematic reviews or meta-analyses also attempted to address the comparative efficacy of some available drugs for ADHD, considering either different formulations of the same drug class (e.g.,²⁷) or different classes and agents (e.g.,²⁸). Such systematic reviews/meta-analyses have relied on comparison of effect sizes from individual RCTs or on the qualitative/quantitative summary of head-to-head studies; most of them focused on the comparison of two drugs only. Overall, evidence from these reviews is inconclusive and/or mixed. For example, while some of them found comparable efficacy between psychostimulants and atomoxetine^{29, 30}, others pointed to significantly higher efficacy of psychostimulants compared to other drug³¹⁻³³.

Therefore, there is a need for meta-analytic evidence that can provide a framework to establish a hierarchy of the efficacy and acceptability/tolerability among the available pharmacological treatments for ADHD, in children as well as in adults. Such evidence would be invaluable in day-to-day clinical practice, where clinicians are faced with selecting specific medications for the treatment of ADHD. Furthermore, given the current debate

around the appropriateness of behavioural interventions vs. medications as first line treatment for ADHD ³⁴, the uncertainty on the efficacy/effectiveness of non-pharmacological treatments for ADHD core symptoms ^{34, 35}, and the increasing trend in the prescription of ADHD medications in some countries ³⁴, an up-to-date and accurate estimate of the efficacy, tolerability and safety of the most common ADHD drugs is paramount from a public health standpoint.

Network Meta-Analysis (NMA) is a statistical method of synthesizing information from a network of trials that have addressed the same question using different interventions ³⁶. A NMA relies on the combination of direct and indirect evidence, which can increase precision while randomization is preserved ³⁷⁻⁴¹. Therefore, compared to standard pairwise meta-analyses, NMA gives a higher degree of precision in the estimation of efficacy and acceptability/tolerability of drugs. A further application of the NMA methodology is the possibility of ranking the interventions included in the network according to their relative efficacy and safety, which in itself is highly relevant for treatment decision making in the daily clinical practice.

NMAs addressing the efficacy and tolerability of medications for other psychiatric disorders have been instrumental in providing novel evidence supporting clinical decision making. For instance, a recent NMA concluded that, with the possible exception of fluoxetine, antidepressants do not seem to offer a clear advantage for the acute treatment of major depressive disorder in children and adolescents ⁴².

Whilst previous or ongoing network meta-analyses focused on children with ADHD only ⁴³⁻⁴⁵ or on the comparison of only two medications in adults ⁴⁶, the present one, to our knowledge, is the first NMA addressing the efficacy and tolerability of a set of ADHD medications in children as well as in adults, using stringent criteria to adhere to the methodological assumptions underpinning the validity of a network meta-analysis (see

below).

Objectives

To rank pharmacological treatments in patients with ADHD, in terms of:

1. Overall efficacy on ADHD core symptoms;
2. Tolerability;
3. Global functioning;
4. Acceptability;
5. Changes in blood pressure and weight.

METHODS

Methods for this systematic review have been developed according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions⁴⁷. This systematic review and NMA is registered in the PROSPERO database (registration number: CRD42014008976).

Types of participants

Inclusion criteria

Studies that include children (≥ 5 and < 12 years), adolescents (≥ 12 and < 18 years) and/or adults (≥ 18 years), either in- or outpatients, who: 1) meet DSM-III, III-R, IV, IV-TR or 5 criteria for a primary diagnosis of ADHD or ICD-10 criteria for a primary diagnosis of HKD (we will not include studies using DSM-II criteria since they did not use standardised criteria). There will be no restriction on ADHD subtype/presentation, gender, IQ or socio-economic status of participants. As for comorbidities, we will include studies in which some, or all, participants have one or more psychiatric or neurological comorbidities (except genetic

syndromes), unless participants were pharmacologically treated during the study for these comorbidities (e.g., antiepileptic drugs for epilepsy or mood stabilizers for bipolar disorders).

Exclusion criteria

We will exclude: 1) studies recruiting patients with a diagnosis of Minimal Brain Dysfunction, which would not be comparable with DSM definitions of ADHD or ICD definitions of HKD; 2) trials in which ADHD is a comorbid disorder secondary to a genetic syndrome; 3) studies enrolling subjects defined as “hyperkinetic” or “hyperactive” without application of standardised diagnostic criteria. (4) studies recruiting patients who were taking ADHD medication prior to entering the study, unless participants completed an appropriate wash out period before starting the study trial (see Table 1 for the details about recommended wash out periods for each individual drug); (5) studies including (a) subjects who previously responded (according to the definition provided in the study) to the same medication tested in the randomised phase (irrespective of washout period) or (b) subjects who were responders or stabilized/optimized to an ADHD medication (where stabilized/optimized means responders) during a run-in/open label phase before of randomisation (irrespective of wash out period); (6) studies in which all included subjects were deemed to be “resistant” to a previous ADHD drug, as this would violate the transitivity assumption of NMA ³⁶.

Types of interventions

We will include studies assessing any of the following drugs, as oral monotherapy (tablets, capsules, chewable compounds or liquid formulations), compared to each other or with placebo: methylphenidate, dexamethylphenidate, atomoxetine, amphetamine derivatives, lisdexamfetamine, clonidine, guanfacine, bupropion, and modafinil. Only studies where medications were given within the licensed or recommended dose level (see Tables 2 and 3),

will be included. Both fixed-dose and flexible-dose designs will be allowed. Studies assessing the efficacy of multimodal treatments including the combination of ADHD drug(s) plus psychotherapy (for ADHD or other disorders/conditions) will be excluded. Studies in which ADHD drugs of interest for the present meta-analysis are combined with psychoeducation only, rather than psychotherapy, will be retained. Study arms with medication only as monotherapy will be included from these studies if comparable with another medication only or placebo arm from the same study. Studies comparing any ADHD drug to treatment as usual or assessing the efficacy of additional drugs in participants resistant to the first ADHD drug will not be included. Studies using a single dose of drug will also be excluded. In terms of minimum duration of the pharmacological treatment, while previous meta-analyses have included studies with treatment duration of 1 day (e.g., ²⁵) and other meta-analyses have excluded studies lasting less than 3 weeks (e.g., ⁴³), we will include trials with treatment duration of at least 7 consecutive days, since response to adequate doses of psychostimulants can be appreciated already after approximately 1 week of treatment and, to our knowledge, there is no clear evidence that placebo effects change over time in studies of ADHD drugs.

Timing of outcome assessment

We will include studies assessing efficacy of drugs both in the short term (outcomes up to 12 weeks) and in the medium term (up to 26 weeks). For short term studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 12 weeks. For medium term studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 26 weeks. We will consider also longer term outcomes (at least 52 weeks). For these studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 52 weeks.

Types of studies

Inclusion criteria

Only double-blinded RCTs will be included. Three types of trials will be eligible for inclusion: parallel-group RCTs, crossover trials and cluster trials. For cross-over studies, to address concerns around possible “carry over” effects ⁴⁸, we will use data from the pre-crossover phase, whenever this is reported in the paper. When data for the pre-cross over phase are not reported, we will contact study authors to gather them. If pre-crossover data are not reported and not available upon request, we will use data at the endpoint (after crossing over), derived from appropriate statistical methods (i.e., paired t-test) ⁴⁹, only if there was a washout period (see Table 1) between the two phases (pre and post crossover) of the trial. As for cluster trials, according to the Cochrane Handbook, they can be combined with individually randomised RCTs ⁵⁰. In this case, approximately correct analyses will be performed by dividing the binary data (the number of participants and the number experiencing the event) as presented in a report by a ‘design effect’ ⁵⁰. This is calculated by using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) (Design effect = 1 + (m - 1) * ICC) ⁵⁰. The ICC will be estimated by using the between-cluster variance component and the within-cluster variance component of the study ⁵¹. For continuous data only, the sample size will be reduced; means and standard deviations will remain unchanged. Data from the withdrawal phase of a trial, in which already treated subjects are randomized to either continue medication or switch to placebo, following an open label phase, will be used only if subjects were not stabilized during the open label phase or if there was a washout period before randomisation to the continuation phase.

Exclusion criteria

Quasi-randomized controlled trials, in which treatment assignment is decided through methods such as alternate days of the week, or studies using Latin square approach without adequate randomisation will be excluded. We will also exclude open-label or single blind RCTs, long-term studies using a maintenance design, and N-of-1 trials.

Types of outcome measures

Primary outcomes

- Efficacy (as continuous outcome) on severity of ADHD core symptoms (total combined, i.e. inattentive plus hyperactive/impulsive symptoms), measured as endpoint score on a standardised scale filled out by parents, teachers, patients or clinician(s). Where there are ratings based on two or more scales, only one scale will be selected among the following ones, in the following order of preference: ADHD Rating Scale (*total score*), SNAP ADHD (*total score*), Conners rating scale (any version, *ADHD total score*), or other ADHD scales. Total scores for ADHD symptoms will be selected and evaluated. However, when total scores are not available and only sub-scales of ADHD measures (i.e., measuring the dimensions of inattention and hyperactivity/impulsivity symptoms of ADHD separately) are reported, the effect size for each of these will be calculated separately and aggregated to estimate the overall effect. When endpoint scores are not reported but change scores are, we will use the latter scores⁵². We will conduct separate analyses for measures rated by 1) clinicians, 2) parents, 3) teachers, and 4) patients (self). Teachers and clinicians' scores will be considered for the primary analysis of studies in children/adolescents and adults, respectively.
- Tolerability of treatment, defined as the proportion of patients who left the study early due to any side effects during the first 12 weeks of treatment.

Secondary outcomes

- Global functioning, measured by the Clinical Global Impressions-Improvement (CGI-I, investigator’s rating) considered at time-points closest to 12 weeks, and, if available, at 26 and 52 weeks. We will consider the proportion of participants who improved at endpoint based on the final CGI-I score of 1-2;
- Acceptability of treatment, defined as the proportion of patients who left the study early for any reason during the first 12 weeks of treatment, consistent with Cipriani et al.⁴²;
- Change in blood pressure (diastolic and systolic), measured in mmHg;
- Change in body weight, measured in Kg.

Search strategy

We will search for both published and unpublished RCTs meeting the inclusion criteria.

Electronic searches

Electronic literature search will be conducted by two members of the Cochrane Schizophrenia Group (FS and JX) with input from the EAGG members. The following search resources will be considered: PubMed, MEDLINE, EMBASE, PsycINFO, ERIC and Web of Science (including Science Citation Index Expanded (SCI-EXPANDED), Social Science Citation Index (SSCI), Conference Proceedings Citation Index- Science (CPCI-S), and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)) via Web of Knowledge. We will also search the following international databases:

1. WHO International Clinical Trials Registry Platform (ICTRP), including:
 - Australian New Zealand Clinical Trials Registry (ANZCTR) (including clinical trials from Therapeutic Goods Administration (TGA))

- *Brazilian Clinical Trials Registry (ReBec)*
 - *Chinese Clinical Trial Register (ChiCTR)*
 - *Clinical Research Information Service (CRiS), Republic of Korea*
 - *ClinicalTrials.gov (including clinical trials from FDA)*
 - *Clinical Trials Registry - India (CTRI)*
 - *Cuban Public Registry of Clinical Trials (RPCEC)*
 - *EU Clinical Trials Register (EU-CTR) (including clinical trials from the European Medicines Agency (EMA))*
 - *German Clinical Trials Register (DRKS)*
 - *Iranian Registry of Clinical Trials (IRCT)*
 - *ISRCTN.org (including clinical trials from controlled-trials.com, The Wellcome Trust (UK), UK trials (UK), Action Medical Research (UK), the Medicines and Healthcare products Regulatory Agency (MHRA), and National Research Register)*
 - *Japan Primary Registries Network (JPRN) (including clinical trials from UMIN-CTR, JapicCTI, and JMACCT)*
 - *Pan African Clinical Trial Registry (PACTR)*
 - *Sri Lanka Clinical Trials Registry (SLCTR)*
 - *The Netherlands National Trial Register (NTR)*
 - *Thai Clinical Trials Register (TCTR)*
2. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
 3. UK Clinical Trials Gateway
 4. BIOSIS Previews via Web of Knowledge
 5. SEAGLE (OpenGrey)

6. ProQuest Theses and Dissertations

7. ClinicalTrials.gov

8. <http://www.fda.gov/>

9. www.ema.europa.eu

The following search terms will be used for 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 Metamphetamine[tiab] OR Deoxyephedrine[tiab] OR Desoxyephedrine[tiab] OR Ecstasy[tiab] OR Atomoxetine[tiab] OR Biphentin[tiab] OR Bupropion[tiab] OR Amfebutamone[tiab] OR Zynatabac[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]) 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])

Search terms and syntax will be adapted as required for each of the databases.

Reference lists and other sources

The references of all selected studies will be searched for other published reports and citations of unpublished studies. Relevant review papers will be checked. In addition, websites of the most relevant pharmaceutical companies manufacturing ADHD drugs will be hand-searched for published, unpublished and ongoing controlled trials. Companies producing ADHD drugs will also be contacted to inquire about any additional relevant study. New trials which have been completed will be included if usable data are provided by the pharmaceutical company.

Identification and selection of studies

Studies identified through electronic and manual searches will be listed with citation, titles and abstracts, in Endnote; duplicates will be excluded using the Endnote function “remove duplicates”. The eligibility for inclusion process will be conducted in two separate stages:

1. Two authors will independently screen title and abstracts of all non-duplicated papers 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, a

third senior author will act as arbitrator. If any doubt about inclusion exists, the article will proceed to the next stage;

2. The full-text version of the articles passing stage 1 screening will be downloaded and assessed for eligibility by two authors, independently. Discrepancies will be resolved by consensus between the two authors and, if needed, a third senior author 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.

Data extraction

The following data will be collected from each included study:

- Study citation, year(s) of study, year of publication, location, setting, number of centres, design (type of RCT), sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Characteristics of study participants, including: gender distribution, mean and range of age, presence and type of co-morbid (neuro)psychiatric conditions, mean (and SD) IQ, number randomised into each group, and number of dropouts, and whether ADHD medications naïve at baseline or previously exposed to other ADHD medications;
- Characteristics of interventions including mean and maximum doses, formulation, add-on interventions (if any), and whether forced dose or optimised treatment;
- Time(s) of outcome measurement;
- Outcome measures reported including whether the data are based on an intention-to-treat (ITT) or completers only sample. For ITT samples, methods of imputation will be noted.

One reviewer will input outcome data into Excel. This will be independently cross-checked by another reviewer. Data from studies included in previous systematic reviews only

will be extracted by one reviewer and independently cross-checked by a second reviewer for accuracy. Degree of agreement between the independent raters will be reported in terms of kappa coefficients and percentage agreements for main outcomes, study and population characteristics and risk of bias items (see below).

Risk of bias assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool, as a reference⁵⁰. The following five domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome: was knowledge of the allocated treatment adequately prevented during the study?
4. Incomplete outcome data for the primary outcomes: were incomplete outcome data adequately addressed?
5. Selective outcome reporting: are reports of the study free from suggestion of selective outcome reporting?

A description of what was reported to have happened in each study will be provided, and a judgment on the risk of bias will be made for each domain, based on the following three categories: "high risk of bias", "low risk of bias" and "unclear risk of bias". The potential bias for "sponsorship bias" will be assessed as a separate item. As in Catala-Lopez et al.⁴³, the overall rating of risk of bias for each study will be the lowest rating for any of the criteria (e.g., if any domain is scored high risk of bias, the study will be considered high risk of bias). Two independent review authors will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreement will be

resolved through discussion and in consultation with the principal investigators. Where necessary, the authors of the studies will be contacted for further information.

Measures of treatment effect

Relative treatment effects

Continuous outcomes: where different measures are used to assess the same outcome, data will be pooled with standardized mean difference (SMD) Hedges’s adjusted g ⁵⁰. Dichotomous outcomes will be analysed by calculating the odds ratio (OR). Results from the NMA will be presented as summary relative effect sizes (SMD or OR) and relative 95% confidence intervals for each possible pair of treatments.

Relative treatment ranking

We will estimate the probability for each intervention to be the best for each outcome, given the relative effect sizes as estimated in NMA. As described in Salanti⁵³, we will obtain a hierarchy of the competing interventions using the Surface Under the Cumulative Ranking curve (SUCRA) and mean ranks. SUCRA values will be expressed as percentage, showing the relative probability of an intervention to be among the best options without uncertainty.

Dealing with missing data

Missing dichotomous outcome data will be managed according to the ITT principle, and it will be assumed that patients in the full analysis set who dropped out after randomization 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 by the trial authors; if LOCF (or other imputation method) data are not available, missing data will be analysed using a validated method. We will use published SD, where

available. If SD are not available from the publication, SD will be calculated from p-values, t-values, confidence intervals or standard errors⁵⁴. If these values are missing, attempts will be made to obtain SD or p-values, t-values, confidence intervals or standard errors from trial authors. Where SDs are not available, a validated method for imputation will be used⁵⁵. We will check that the original SDs are normally distributed, so that the imputed SD represents the average. Where imputation is employed, data will be interpreted with caution, and the degree of heterogeneity observed will need to be taken into account when interpreting findings. A sensitivity analysis will also be undertaken to examine the effect of imputation of the findings.

Assessment of clinical and methodological heterogeneity within treatment comparisons

The studies synthesized in each pairwise comparison need to be similar enough in terms of patient characteristics, setting, and outcome definitions, among others, in order to obtain interpretable and useful results⁵⁰. To evaluate the degree of clinical and methodological heterogeneity, we will generate descriptive statistics for trial and study population characteristics across all eligible trials. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics⁵⁰.

Assessment of transitivity across treatment comparisons

The assumption of transitivity underlies NMA and needs careful evaluation. In the case that transitivity is not plausible in a network of trials, the indirect and mixed treatment effect estimates are not valid. To infer about the assumption of transitivity⁵⁶:

1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs;

2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons. If the distributions are balanced across comparisons, we will conclude against evidence of intransitivity⁵⁷.

Data analysis

Synthesis of results

First, pairwise meta-analyses will be conducted for all outcomes and comparisons at each time point, using a random-effects model⁵⁸. Then, a NMA will be performed within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons and accounting for correlations induced by multi-arm studies^{56, 59}. Both pairwise meta-analysis and NMA will be performed for children/adolescents and adults, respectively. The analysis will be performed using STATA v.13. (MRC Biostatistics Unit, Cambridge, UK, <http://cmimg.cochrane.org/network-meta-analysis-toolkit>); the codes and description of the methodology can be found in <http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis>⁶⁰⁻⁶². Studies in children and adolescents will be combined in the statistical analyses. For primary outcomes, we will also assess the quality of evidence using GRADE⁶³ (GRADE Working Group 2004)⁶³. The criteria considered are: study limitations, indirectness, inconsistency, imprecision, and reporting bias. We will assign four levels of quality of evidence: *high, moderate, low, and very low*.

Assessment of statistical heterogeneity

In standard pairwise meta-analyses, we will estimate different heterogeneity variances for each pairwise comparison. In network meta-analysis, we will assume a common estimate for the heterogeneity variance (τ^2) within and across comparisons. The presence of statistical heterogeneity within each pairwise comparison will be assessed by visual inspection of the

forest plots and by calculating the I-squared statistic and its confidence limits⁶⁴. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the common τ^2 estimated from the NMA models⁶⁵. For dichotomous outcomes, the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner et al.⁶⁶.

Assessment of statistical incoherence

Local and global approaches will be used to evaluate statistical incoherence. To evaluate the presence of incoherence locally, we will use the loop-specific approach⁶⁷. This method evaluates the incoherence assumption by calculating the incoherence factor as the difference between direct and indirect estimates for a specific comparison in each closed loop formed by the network of trials (using the Bucher method) and their relative 95% confidence intervals. The incoherence factor is the logarithm of the ratio of two risk ratios (RRR) from direct and indirect evidence in the loop. Then we will examine whether there are any material discrepancies; if the 95% CI does overlap with 1, the hypothesis of incoherence is not rejected, as described in Salanti⁶⁸. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using the 'ifplot' command in STATA. To check the assumption of consistency in the entire network, we will use the 'design-by-treatment' model⁶⁹. This method accounts for different source of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer the presence of inconsistency from any source in the entire network based on a chi-square test. The design-by-treatment model will be performed in STATA using the 'mvmeta' command. Inconsistency and heterogeneity are interweaved; to distinguish between these two sources of variability we will employ the I-squared for

inconsistency that measures the percentage of variability that cannot be attributed to random error or heterogeneity (within comparison variability) ⁶⁵.

Investigation of heterogeneity and inconsistency

In the case of important clinical or statistical inconsistency, the feasibility of multiple-treatments meta-regression or subgroup analysis will be considered to investigate the possible sources of heterogeneity and incoherence by using the following effect modifiers (for primary outcomes only):

1. studies sponsored vs. those not sponsored by pharmaceutical companies;
2. males vs. females;
3. children vs. adolescents, since some medications (e.g., SSRIs) have been reported to have different efficacy in children vs. adolescents ⁷⁰; [it will be to include in this analysis studies assessing, e.g., individuals aged 10-14 years, unless data separately for children (aged < 12 years), and adolescents (aged ≥ 12) are obtained].

Sensitivity analyses

We will explore the feasibility of conducting the following sensitivity analyses by excluding:

- 1) studies where all participants have IQ < 70;
- 2) studies where all participants have psychiatric/neurologic comorbidities;
- 3) studies lasting less than 2 weeks;
- 4) studies for which imputation of missing data was required;
- 5) studies with overall high or unclear risk of bias;
- 6) cross-over trials;
- 7) studies including patients resistant to ADHD medication;

8) studies recruiting only non-treatment-naïve patients;

7) A final sensitivity analysis will address whether unbalanced doses affected the results. To exclude trials with non-equivalent comparisons, we will apply a previously validated approach used for antidepressant trials⁷¹. For this, we put together a roster (see Table 2 and 3) in which low and high doses of the drugs included in the present NMA are described. Table 2 is based on FDA indications. This roster will be employed to detect inequalities in dosing that could affect comparative efficacy by excluding trials with low doses of one drug and high doses of the other (or vice-versa). We will not consider starting doses if these were supposed to be increased during the trial.

ETHICS AND DISSEMINATION

No ethical issues are foreseen since ethical approval has been obtained for each study that will be included in the systematic review/meta-analysis. The results of this study will be published in a peer-reviewed journal and will be also possibly presented at national and international meetings of (child) psychiatry, psychology, and paediatrics.

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GUARANTOR OF THE REVIEW: Dr. Samuele Cortese

AUTHORS' CONTRIBUTION: Dr Cortese drafted the protocol (except the literature search and statistical analysis sections). Drs. Shokrane and Xia drafted the literature search

section. Dr. Del Giovane drafted the statistical analysis section. All other co-authors critically reviewed the protocol and amended it.

COMPETING INTEREST STATEMENT

Dr. Cortese has received reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non profit organization, in relation to lectures that he delivered for ACAMH.

Dr. Mohr-Jensen has been a speaker for HB Pharma/Medice.

Dr. Carucci collaborated within projects from the European Union (7FP) and has received travel support from Shire Pharmaceutical Company; she collaborated as sub-investigator in sponsored clinical trial by Shire Pharmaceutical Company.

Dr. Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, Otsuka, PCM scientific, Shire and Viforpharma. He received conference support or speaker’s fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press.

Dr. Zuddas has received honoraria for participating to Advisory board or Data Safety Monitory Boards from Eli Lilly, Otsuka, Lundbeck, Takeda and EduPharma. He has also received royalties from Oxford University Press and Giunti OS, and research grants from Lundbeck, Roche, Shire and Vifor.

Dr. Steinhausen has worked as an advisor and speaker for the following pharmaceutical companies: Janssen-Cilag, Eli Lilly, Novartis, Medice, Shire, and UCB and has also received unrestricted grants for postgraduate training courses or conferences and research by Janssen-Cilag, Eli Lilly, Novartis, Medice, and Swedish Orphan International. He receives book

royalties from Cambridge University Press, Elsevier, Hogrefe, Huber, Klett, and Kohlhammer publishers.

Dr. Cipriani has served as an expert witness for a patent litigation case about quetiapine extended-release and is supported by the NIHR Oxford Cognitive Health Clinical Research Facility.

Dr. Coghill reports grants and personal fees from Shire, personal fees from Eli Lilly, grants from Vifor, personal fees from Novartis, personal fees from Oxford University Press.

Drs. Adamo, Hayes, Bhatti, Del Giovane, Atkinson, Simonoff, Barbui, Purgato, Shokraneh and Xia report no competing conflicts of interest.

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Table 1. Washout periods.

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

Table 2. Dose range of medication included in the network meta-analysis for children/adolescents, according to the FDA whenever possible (as retrieved in <https://dailymed.nlm.nih.gov/dailymed/> or <http://www.accessdata.fda.gov/>; other source: Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attentiondeficit/hyperactivity disorder: emerging concepts from new data. J Child Adolesc Psychopharmacol 2007;17:393-406)

Drug	Min. daily dose	Max. daily dose
Methylphenidate hydrochloride immediate release	10 mg	60 mg
Methylphenidate hydrochloride intermediate acting	20 mg	60 mg
Methylphenidate hydrochloride long acting	18 mg	54 mg (children) 72 mg (adolescents) (do not exceed 2 mg/Kg/day)
Methylphenidate hydrochloride oral solution	10 mg	60 mg
Methylphenidate hydrochloride chewable tablets	10 mg	60 mg
d,l-threo Methylphenidate slow release	20 mg	60 mg
Dexmethylphenidate (d-threo-methylphenidate) immediate release	5 mg	20 mg
Dexmethylphenidate (d-threo-methylphenidate) XR	5 mg (children)	20 mg
Dextro-amphetamine immediate release	2.5 mg (children 3-5 y) 5 mg (children \geq 6 y)	Children 3-5 y: not specified Children \geq 6 y: 40 mg
Dextro-amphetamine ER	10 mg (children 6-12 y and adolescents 13-17 y)	30 mg (children 6-12 y) Adolescents: not specified
Mixed Amphetamine Salts	2.5 mg (children 3-5 y) 5 mg (children \geq 6 y)	40 mg (children \geq 6 y)
Mixed Amphetamine Salts XR	10 mg (children \geq 6 y) 10 mg, increased to 20 mg (adolescents 13-17 y)	30 mg (children \geq 6 y) Adolescents 13-17 y and
Lisdexamfetamine	30 mg (individuals \geq 6 y)	70 mg (individuals \geq 6 y)
Atomoxetine	0.5 mg/Kg (children and adolescents \leq 70 Kg) 40 mg (children and adolescents $>$ 70 Kg and adults)	1.4 (1.8 in Europe) mg/Kg or 100 mg, whichever less (children and adolescents \leq 70 Kg) 100 mg (children and adolescents $>$ 70 Kg)
Clonidine immediate release	Children/adolescents $<$ 45 Kg: 0.05 mg	Children/adolescents $<$ 45 Kg: 0.2 mg

	Children/adolescents > 45 Kg: 0.1 mg	Children/adolescents > 45 Kg: 0.4 mg
Clonidine extended release	0.1 mg	0.4 mg
Guanfacine immediate release	0.5 mg	N/S
Guanfacine extended release	1 mg	7 mg
Bupropion IR	N/S	N/S
Bupropion SR	N/S	N/S
Bupropion XL	N/S	N/S
Modafinil	200 mg	400 mg

Table 3. Dose range of medication included in the network meta-analysis for adults, according to the FDA whenever possible (as retrieved in <https://dailymed.nlm.nih.gov/dailymed/> or <http://www.accessdata.fda.gov/>; other sources: <http://integratedcare-nw.org/docs/PCPtraining/AdultADHDSummary-Recommendations.pdf>; Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attention deficit/hyperactivity disorder: emerging concepts from new data. *J Child Adolesc Psychopharmacol* 2007;17:393-406)

Drug	Min. daily dose	Max. daily dose
Methylphenidate hydrochloride immediate release	10 mg	60 mg
Methylphenidate hydrochloride intermediate acting	20 mg	60 mg
Methylphenidate hydrochloride long acting	18-36 mg	72 mg
Methylphenidate hydrochloride oral solution	10 mg	60 mg
Methylphenidate hydrochloride chewable tablets	10 mg	60 mg
d,l-threo Methylphenidate slow release	20 mg	60 mg
Dexmethylphenidate (d-threo-methylphenidate) immediate release	5 mg	20 mg
Dexmethylphenidate (d-threo-methylphenidate) XR	10 mg (adult)	20 mg
Dextro-amphetamine immediate release	N/S	N/S
Dextro-amphetamine ER	20 mg	N/S
Mixed Amphetamine Salts	N/S	N/S
Mixed Amphetamine Salts XR	20 mg	N/S
Lisdexamfetamine	30 mg	70 mg
Atomoxetine	N/S	100 mg
Clonidine immediate release	N/S	N/S
Clonidine extended release	0.1 mg	0.4 mg
Guanfacine immediate release	0.5 mg	N/S
Guanfacine extended release	1 mg	7 mg
Bupropion IR	100 mg bid	100 mg tid

Bupropion SR	150 mg qam	150 mg bid
Bupropion XL	150 mg qam	300 mg qam
Modafinil	200 mg	400 mg

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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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review: Pag. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Pag. 5 and 8
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Pag. 1-3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review. Pag. 24
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review Pag. 24
Sponsor	5b	Provide name for the review funder and/or sponsor Pag. 24
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Pag. 24
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Pag.6-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Pag. 8
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 Pag.8-13
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 Pag. 13-17
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 Pag. 15
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Pag. 16-18

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) Pag. 16-17
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 Pag. 17-18
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 Pag. 17-18
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Pag. 12-13
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 Pag. 18-19
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Pag. 21
	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) Pag. 21-23
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Pag. 23-24
	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) Pag. 23
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Pag. 21

*** 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.**

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Comparative efficacy and tolerability of pharmacological interventions for Attention-Deficit/Hyperactivity Disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis



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Secondary Subject Heading:	Mental health
Keywords:	Attention-Deficit/Hyperactivity Disorder, pharmacological treatment, acute treatment, systematic review, network meta-analysis

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**Comparative efficacy and tolerability of pharmacological interventions for
Attention-Deficit/Hyperactivity Disorder in children, adolescents and adults:
protocol for a systematic review and network meta-analysis**

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Keywords: Attention-Deficit/Hyperactivity Disorder; ADHD; children; adolescents; adults; pharmacological treatment; acute treatment; systematic review; network meta-analysis.

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ABSTRACT

Introduction: Attention-Deficit/Hyperactivity Disorder (ADHD) is a major public health issue. Pharmacological treatments play an important role in the multimodal treatment of ADHD. Currently, there is a lack of up-to-date and comprehensive evidence on how available ADHD drugs compare and rank in terms of efficacy and tolerability, in children or adolescents as well as in adults. We will conduct a network meta-analysis (NMA), integrating direct and indirect comparisons from randomised controlled trials (RCTs), to rank pharmacological treatments for ADHD according to their efficacy and tolerability profiles.

Methods and analysis: We will search a broad range of electronic databases, including PubMed, MEDLINE, EMBASE, PsycINFO, ERIC, and Web of Science, with no date or language restrictions. We will also search for unpublished studies using international clinical trial registries and contacting relevant drug companies. We will identify and include available parallel-group, cross-over and cluster randomised trials that compare methylphenidate, dexamethylphenidate, amphetamine derivatives, lisdexamfetamine, atomoxetine, clonidine, guanfacine, bupropion, or modafinil (as oral therapy) either with each other or to placebo, in children, adolescents or adults with ADHD. Primary outcomes will be efficacy (indicated by reduction in severity of ADHD core symptoms measured on a standardised scale) and tolerability (the proportion of patients who left a study early due to side effects). Secondary outcomes will be global functioning, acceptability (proportion of patients who left the study early by any cause), and changes in blood pressure and body weight. NMA will be conducted in STATA within a frequentist framework. The quality of RCTs will be evaluated using the Cochrane risk of bias tool, and the quality of the evidence will be assessed using the GRADE approach. Subgroup and sensitivity analyses will be conducted to assess the robustness of the findings. **Ethics and dissemination:** No ethical issues are foreseen. Results from this study will be published in a peer-reviewed journal and possibly presented at relevant national and

international conferences. **Registration:** PROSPERO-National Institute of Health Research (NIHR) Prospective Register of Systematic Reviews (CRD42014008976).

Strengths and limitations of the study

Strengths:

- This is the first comprehensive network meta-analysis addressing the efficacy and tolerability of medications for ADHD in children, adolescents and adults. By integrating direct and indirect evidence from all included studies, it will increase the precision of treatment estimates and allow for the ranking of available ADHD drugs in terms of both efficacy and acceptability;
- Subgroup and sensitivity analyses will address important clinical questions (e.g., differences between sexes comparisons between children and adolescents, and subgroup analysis in participants without neurologic/psychiatric comorbidities);
- The findings of this network meta-analysis have the potential to inform and influence both clinical decision making and guideline development.

Limitations:

- As with any meta-analysis, the present one will be limited by the quality of the primary studies included in the systematic review. To properly address this issue, we will assess the quality of the studies included in the systematic review and the quality of the evidence using the Cochrane risk of bias tool and the GRADE approach, respectively, that are considered the gold standard for critical appraisal and quality of evidence.

BACKGROUND

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder ¹, characterised, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) ², by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. Hyperkinetic Disorder (HKD), as defined in the International Classification of Diseases, 10th Edition (ICD-10) ³, is a narrower diagnostic category, requiring both symptoms of inattention and hyperactivity/impulsivity, similarly to those individuals meeting criteria for the combined presentation of ADHD as per DSM-5 ². A large body of evidence shows that ADHD is frequently comorbid with other psychiatric conditions, the most common of which include oppositional defiant disorder, conduct disorder, specific learning disorders, mood and anxiety disorders, substance use disorders, sleep disturbances and other neurodevelopmental disorders such as autism spectrum disorder ^{4, 5}. The worldwide-pooled prevalence of ADHD is estimated at around 5% in school-age children ^{1, 6}, albeit with a substantial heterogeneity between studies, accounted for by differences in either the method of assessment or the diagnostic criteria employed. Impairing symptoms of ADHD persist into adulthood in around 65% of cases ⁷, with a pooled prevalence of adulthood ADHD around 2.5% ⁸. As a consequence of the nature of the core symptoms and the comorbid disorders, ADHD imposes a substantial burden on society in terms of psychological dysfunction, adverse educational and vocational outcomes, stress on families, and societal financial costs. Average annual incremental costs of ADHD have been estimated at \$143-\$266 billion in the U.S. ⁹ and are substantial in other countries as well (e.g., ^{10, 11}).

Available treatments for ADHD include pharmacological and non-pharmacological interventions. Pharmacological treatments are recommended as the first option in several guidelines/practice parameters (e.g., ¹²), at least for severe cases ^{13, 14}, or as a treatment strategy for patients who have not responded to non-pharmacological interventions ^{13, 14}.

Medications for ADHD include psychostimulant (e.g., methylphenidate and amphetamine derivatives) and non-psychostimulant drugs (e.g., atomoxetine, clonidine and guanfacine, among others). A large body of evidence from double-blind randomized controlled trials (RCTs), summarized in several meta-analyses in children, adolescents and/or adults, demonstrated that different classes of psychostimulants (e.g., methylphenidate¹⁵⁻¹⁸ or mixed amphetamine salts¹⁹ and other amphetamine derivatives²⁰) and some non-psychostimulant treatments, such as atomoxetine²¹⁻²⁴, are significantly more efficacious than placebo, at least in the short term, when considering ADHD core symptoms as main outcome. However, two recent Cochrane reviews^{25, 26} have questioned the quality of the evidence from the available RCTs, in contrast with a previous review by the National Institute for Health and Care Excellence (NICE)¹³, that assessed the quality of the evidence as *high*.

Importantly, previous systematic reviews or meta-analyses also attempted to address the comparative efficacy of some available drugs for ADHD, considering either different formulations of the same drug class (e.g.,²⁷) or different classes and agents (e.g.,²⁸). Such systematic reviews/meta-analyses have relied on comparison of effect sizes from individual RCTs or on the qualitative/quantitative summary of head-to-head studies; most of them focused on the comparison of two drugs only. Overall, evidence from these reviews is inconclusive and/or mixed. For example, while some of them found comparable efficacy between psychostimulants and atomoxetine^{29, 30}, others pointed to significantly higher efficacy of psychostimulants compared to other drug³¹⁻³³.

Therefore, there is a need for meta-analytic evidence that can provide a framework to establish a hierarchy of the efficacy and acceptability/tolerability among the available pharmacological treatments for ADHD, in children as well as in adults. Such evidence would be invaluable in day-to-day clinical practice, where clinicians are faced with selecting specific medications for the treatment of ADHD. Furthermore, given the current debate

around the appropriateness of behavioural interventions *vs.* medications as first line treatment for ADHD ³⁴, the uncertainty on the efficacy/effectiveness of non-pharmacological treatments for ADHD core symptoms ^{34, 35}, and the increasing trend in the prescription of ADHD medications in some countries ³⁴, an up-to-date and accurate estimate of the efficacy, tolerability and safety of the most common ADHD drugs is paramount from a public health standpoint.

Network Meta-Analysis (NMA) is a statistical method of synthesizing information from a network of trials that have addressed the same question using different interventions ³⁶. A NMA relies on the combination of direct and indirect evidence, which can increase precision while randomization is preserved ³⁷⁻⁴¹. Therefore, compared to standard pairwise meta-analyses, NMA gives a higher degree of precision in the estimation of efficacy and acceptability/tolerability of drugs. A further application of the NMA methodology is the possibility of ranking the interventions included in the network according to their relative efficacy and safety, which in itself is highly relevant for treatment decision making in the daily clinical practice.

NMAs addressing the efficacy and tolerability of medications for other psychiatric disorders have been instrumental in providing novel evidence supporting clinical decision making. For instance, a recent NMA concluded that, with the possible exception of fluoxetine, antidepressants do not seem to offer a clear advantage for the acute treatment of major depressive disorder in children and adolescents ⁴².

Whilst previous or ongoing network meta-analyses focused on children with ADHD only ⁴³⁻⁴⁵ or on the comparison of only two medications in adults ⁴⁶, the present one, to our knowledge, is the first NMA addressing the efficacy and tolerability of a set of ADHD medications in children as well as in adults, using stringent criteria to adhere to the methodological assumptions underpinning the validity of a network meta-analysis (see

below).

Objectives

To rank pharmacological treatments in patients with ADHD, in terms of:

1. Overall efficacy on ADHD core symptoms;
2. Tolerability;
3. Global functioning;
4. Acceptability;
5. Changes in blood pressure and weight.

METHODS

Methods for this systematic review have been developed according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions⁴⁷. This systematic review and NMA is registered in the PROSPERO database (registration number: CRD42014008976).

Types of participants

Inclusion criteria

Studies that include children (≥ 5 and < 12 years), adolescents (≥ 12 and < 18 years) and/or adults (≥ 18 years), either in- or outpatients, who: 1) meet DSM-III, III-R, IV, IV-TR or 5 criteria for a primary diagnosis of ADHD or ICD-10 criteria for a primary diagnosis of HKD (we will not include studies using DSM-II criteria since they did not use standardised criteria). There will be no restriction on ADHD subtype/presentation, gender, IQ or socio-economic status of participants. As for comorbidities, we will include studies in which some, or all, participants have one or more psychiatric or neurological comorbidities (except genetic

syndromes), unless participants were pharmacologically treated during the study for these comorbidities (e.g., antiepileptic drugs for epilepsy or mood stabilizers for bipolar disorders).

Exclusion criteria

We will exclude: 1) studies recruiting patients with a diagnosis of Minimal Brain Dysfunction, which would not be comparable with DSM definitions of ADHD or ICD definitions of HKD; 2) trials in which ADHD is a comorbid disorder secondary to a genetic syndrome; 3) studies enrolling subjects defined as “hyperkinetic” or “hyperactive” without application of standardised diagnostic criteria. (4) studies recruiting patients who were taking ADHD medication prior to entering the study, unless participants completed an appropriate wash out period before starting the study trial (see Table 1 for the details about recommended wash out periods for each individual drug); (5) studies including (a) subjects who previously responded (according to the definition provided in the study) to the same medication tested in the randomised phase (irrespective of washout period) or (b) subjects who were responders or stabilized/optimized to an ADHD medication (where stabilized/optimized means responders) during a run-in/open label phase before of randomisation (irrespective of wash out period); (6) studies in which all included subjects were deemed to be “resistant” to a previous ADHD drug, as this would violate the transitivity assumption of NMA ³⁶.

Types of interventions

We will include studies assessing any of the following drugs, as oral monotherapy (tablets, capsules, chewable compounds or liquid formulations), compared to each other or with placebo: methylphenidate, dexamethylphenidate, atomoxetine, amphetamine derivatives, lisdexamfetamine, clonidine, guanfacine, bupropion, and modafinil. Only studies where medications were given within the licensed or recommended dose level (see Tables 2 and 3),

will be included. Both fixed-dose and flexible-dose designs will be allowed. Studies assessing the efficacy of multimodal treatments including the combination of ADHD drug(s) plus psychotherapy (for ADHD or other disorders/conditions) will be excluded. Studies in which ADHD drugs of interest for the present meta-analysis are combined with psychoeducation only, rather than psychotherapy, will be retained. Study arms with medication only as monotherapy will be included from these studies if comparable with another medication only or placebo arm from the same study. Studies comparing any ADHD drug to treatment as usual or assessing the efficacy of additional drugs in participants resistant to the first ADHD drug will not be included. Studies using a single dose of drug will also be excluded. In terms of minimum duration of the pharmacological treatment, while previous meta-analyses have included studies with treatment duration of 1 day (e.g., ²⁵) and other meta-analyses have excluded studies lasting less than 3 weeks (e.g., ⁴³), we will include trials with treatment duration of at least 7 consecutive days, since response to adequate doses of psychostimulants can be appreciated already after approximately 1 week of treatment and, to our knowledge, there is no clear evidence that placebo effects change over time in studies of ADHD drugs.

Timing of outcome assessment

We will include studies assessing efficacy of drugs both in the short term (outcomes up to 12 weeks) and in the medium term (up to 26 weeks). For short term studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 12 weeks. For medium term studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 26 weeks. We will consider also longer term outcomes (at least 52 weeks). For these studies, if outcomes at different or several time-points are reported, we will choose the outcomes at the time-point closest to 52 weeks.

Types of studies

Inclusion criteria

Only double-blinded RCTs will be included. Three types of trials will be eligible for inclusion: parallel-group RCTs, crossover trials and cluster trials. For cross-over studies, to address concerns around possible “carry over” effects ⁴⁸, we will use data from the pre-crossover phase, whenever this is reported in the paper. When data for the pre-cross over phase are not reported, we will contact study authors to gather them. If pre-crossover data are not reported and not available upon request, we will use data at the endpoint (after crossing over), derived from appropriate statistical methods (i.e., paired t-test) ⁴⁹, only if there was a washout period (see Table 1) between the two phases (pre and post crossover) of the trial. As for cluster trials, according to the Cochrane Handbook, they can be combined with individually randomised RCTs ⁵⁰. In this case, approximately correct analyses will be performed by dividing the binary data (the number of participants and the number experiencing the event) as presented in a report by a ‘design effect’ ⁵⁰. This is calculated by using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) (Design effect = 1 + (m - 1) * ICC) ⁵⁰. The ICC will be estimated by using the between-cluster variance component and the within-cluster variance component of the study ⁵¹. For continuous data only, the sample size will be reduced; means and standard deviations will remain unchanged. Data from the withdrawal phase of a trial, in which already treated subjects are randomized to either continue medication or switch to placebo, following an open label phase, will be used only if subjects were not stabilized during the open label phase or if there was a washout period before randomisation to the continuation phase.

Exclusion criteria

Quasi-randomized controlled trials, in which treatment assignment is decided through methods such as alternate days of the week, or studies using Latin square approach without adequate randomisation will be excluded. We will also exclude open-label or single blind RCTs, long-term studies using a maintenance design, and N-of-1 trials.

Types of outcome measures

Primary outcomes

- Efficacy (as continuous outcome) on severity of ADHD core symptoms (total combined, i.e. inattentive plus hyperactive/impulsive symptoms), measured as endpoint score on a standardised scale filled out by parents, teachers, patients or clinician(s). Where there are ratings based on two or more scales, only one scale will be selected among the following ones, in the following order of preference: ADHD Rating Scale (*total score*), SNAP ADHD (*total score*), Conners rating scale (any version, *ADHD total score*), or other ADHD scales. Total scores for ADHD symptoms will be selected and evaluated. However, when total scores are not available and only sub-scales of ADHD measures (i.e., measuring the dimensions of inattention and hyperactivity/impulsivity symptoms of ADHD separately) are reported, the effect size for each of these will be calculated separately and aggregated to estimate the overall effect. When endpoint scores are not reported but change scores are, we will use the latter scores⁵². We will conduct separate analyses for measures rated by 1) clinicians, 2) parents, 3) teachers, and 4) patients (self). Teachers and clinicians' scores will be considered for the primary analysis of studies in children/adolescents and adults, respectively.
- Tolerability of treatment, defined as the proportion of patients who left the study early due to any side effects during the first 12 weeks of treatment.

Secondary outcomes

- Global functioning, measured by the Clinical Global Impressions-Improvement (CGI-I, investigator’s rating) considered at time-points closest to 12 weeks, and, if available, at 26 and 52 weeks. We will consider the proportion of participants who improved at endpoint based on the final CGI-I score of 1-2;
- Acceptability of treatment, defined as the proportion of patients who left the study early for any reason during the first 12 weeks of treatment, consistent with Cipriani et al.⁴²;
- Change in blood pressure (diastolic and systolic), measured in mmHg;
- Change in body weight, measured in Kg.

Search strategy

We will search for both published and unpublished RCTs meeting the inclusion criteria.

Electronic searches

Electronic literature search will be conducted by two members of the Cochrane Schizophrenia Group (FS and JX) with input from the EAGG members. The following search resources will be considered: PubMed, MEDLINE, EMBASE, PsycINFO, ERIC and Web of Science (including Science Citation Index Expanded (SCI-EXPANDED), Social Science Citation Index (SSCI), Conference Proceedings Citation Index- Science (CPCI-S), and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)) via Web of Knowledge. We will also search the following international databases:

1. WHO International Clinical Trials Registry Platform (ICTRP), including:
 - Australian New Zealand Clinical Trials Registry (ANZCTR) (including clinical trials from Therapeutic Goods Administration (TGA))

- *Brazilian Clinical Trials Registry (ReBec)*
 - *Chinese Clinical Trial Register (ChiCTR)*
 - *Clinical Research Information Service (CRiS), Republic of Korea*
 - *ClinicalTrials.gov (including clinical trials from FDA)*
 - *Clinical Trials Registry - India (CTRI)*
 - *Cuban Public Registry of Clinical Trials (RPCEC)*
 - *EU Clinical Trials Register (EU-CTR) (including clinical trials from the European Medicines Agency (EMA))*
 - *German Clinical Trials Register (DRKS)*
 - *Iranian Registry of Clinical Trials (IRCT)*
 - *ISRCTN.org (including clinical trials from controlled-trials.com, The Wellcome Trust (UK), UK trials (UK), Action Medical Research (UK), the Medicines and Healthcare products Regulatory Agency (MHRA), and National Research Register)*
 - *Japan Primary Registries Network (JPRN) (including clinical trials from UMIN-CTR, JapicCTI, and JMACCT)*
 - *Pan African Clinical Trial Registry (PACTR)*
 - *Sri Lanka Clinical Trials Registry (SLCTR)*
 - *The Netherlands National Trial Register (NTR)*
 - *Thai Clinical Trials Register (TCTR)*
2. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
 3. UK Clinical Trials Gateway
 4. BIOSIS Previews via Web of Knowledge
 5. SEAGLE (OpenGrey)

6. ProQuest Theses and Dissertations

7. ClinicalTrials.gov

8. <http://www.fda.gov/>

9. www.ema.europa.eu

The following search terms will be used for 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 Metamphetamine[tiab] OR Deoxyephedrine[tiab] OR Desoxyephedrine[tiab] OR Ecstasy[tiab] OR Atomoxetine[tiab] OR Biphentin[tiab] OR Bupropion[tiab] OR Amfebutamone[tiab] OR Zynatabac[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]) 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])

Search terms and syntax will be adapted as required for each of the databases.

Reference lists and other sources

The references of all selected studies will be searched for other published reports and citations of unpublished studies. Relevant review papers will be checked. In addition, websites of the most relevant pharmaceutical companies manufacturing ADHD drugs will be hand-searched for published, unpublished and ongoing controlled trials. Companies producing ADHD drugs will also be contacted to inquire about any additional relevant study. New trials which have been completed will be included if usable data are provided by the pharmaceutical company.

Identification and selection of studies

Studies identified through electronic and manual searches will be listed with citation, titles and abstracts, in Endnote; duplicates will be excluded using the Endnote function “remove duplicates”. The eligibility for inclusion process will be conducted in two separate stages:

1. Two authors will independently screen title and abstracts of all non-duplicated papers 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, a

third senior author will act as arbitrator. If any doubt about inclusion exists, the article will proceed to the next stage;

2. The full-text version of the articles passing stage 1 screening will be downloaded and assessed for eligibility by two authors, independently. Discrepancies will be resolved by consensus between the two authors and, if needed, a third senior author 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.

Data extraction

The following data will be collected from each included study:

- Study citation, year(s) of study, year of publication, location, setting, number of centres, design (type of RCT), sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Characteristics of study participants, including: gender distribution, mean and range of age, presence and type of co-morbid (neuro)psychiatric conditions, mean (and SD) IQ, number randomised into each group, and number of dropouts, and whether ADHD medications naïve at baseline or previously exposed to other ADHD medications;
- Characteristics of interventions including mean and maximum doses, formulation, add-on interventions (if any), and whether forced dose or optimised treatment;
- Time(s) of outcome measurement;
- Outcome measures reported including whether the data are based on an intention-to-treat (ITT) or completers only sample. For ITT samples, methods of imputation will be noted.

One reviewer will input outcome data into Excel. This will be independently cross-checked by another reviewer. Data from studies included in previous systematic reviews only

will be extracted by one reviewer and independently cross-checked by a second reviewer for accuracy. Degree of agreement between the independent raters will be reported in terms of kappa coefficients and percentage agreements for main outcomes, study and population characteristics and risk of bias items (see below).

Risk of bias assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool, as a reference⁵⁰. The following five domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome: was knowledge of the allocated treatment adequately prevented during the study?
4. Incomplete outcome data for the primary outcomes: were incomplete outcome data adequately addressed?
5. Selective outcome reporting: are reports of the study free from suggestion of selective outcome reporting?

A description of what was reported to have happened in each study will be provided, and a judgment on the risk of bias will be made for each domain, based on the following three categories: "high risk of bias", "low risk of bias" and "unclear risk of bias". The potential bias for "sponsorship bias" will be assessed as a separate item. As in Catala-Lopez et al.⁴³, the overall rating of risk of bias for each study will be the lowest rating for any of the criteria (e.g., if any domain is scored high risk of bias, the study will be considered high risk of bias). Two independent review authors will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreement will be

resolved through discussion and in consultation with the principal investigators. Where necessary, the authors of the studies will be contacted for further information.

Measures of treatment effect

Relative treatment effects

Continuous outcomes: where different measures are used to assess the same outcome, data will be pooled with standardized mean difference (SMD) Hedges’s adjusted g ⁵⁰. Dichotomous outcomes will be analysed by calculating the odds ratio (OR). Results from the NMA will be presented as summary relative effect sizes (SMD or OR) and relative 95% confidence intervals for each possible pair of treatments.

Relative treatment ranking

We will estimate the probability for each intervention to be the best for each outcome, given the relative effect sizes as estimated in NMA. As described in Salanti⁵³, we will obtain a hierarchy of the competing interventions using the Surface Under the Cumulative Ranking curve (SUCRA) and mean ranks. SUCRA values will be expressed as percentage, showing the relative probability of an intervention to be among the best options without uncertainty.

Dealing with missing data

Missing dichotomous outcome data will be managed according to the ITT principle, and it will be assumed that patients in the full analysis set who dropped out after randomization 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 by the trial authors; if LOCF (or other imputation method) data are not available, missing data will be analysed using a validated method. We will use published SD, where

available. If SD are not available from the publication, SD will be calculated from p-values, t-values, confidence intervals or standard errors⁵⁴. If these values are missing, attempts will be made to obtain SD or p-values, t-values, confidence intervals or standard errors from trial authors. Where SDs are not available, a validated method for imputation will be used⁵⁵. We will check that the original SDs are normally distributed, so that the imputed SD represents the average. Where imputation is employed, data will be interpreted with caution, and the degree of heterogeneity observed will need to be taken into account when interpreting findings. A sensitivity analysis will also be undertaken to examine the effect of imputation of the findings.

Assessment of clinical and methodological heterogeneity within treatment comparisons

The studies synthesized in each pairwise comparison need to be similar enough in terms of patient characteristics, setting, and outcome definitions, among others, in order to obtain interpretable and useful results⁵⁰. To evaluate the degree of clinical and methodological heterogeneity, we will generate descriptive statistics for trial and study population characteristics across all eligible trials. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics⁵⁰.

Assessment of transitivity across treatment comparisons

The assumption of transitivity underlies NMA and needs careful evaluation. In the case that transitivity is not plausible in a network of trials, the indirect and mixed treatment effect estimates are not valid. To infer about the assumption of transitivity⁵⁶:

1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs;

2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons. If the distributions are balanced across comparisons, we will conclude against evidence of intransitivity⁵⁷.

Data analysis

Synthesis of results

First, pairwise meta-analyses will be conducted for all outcomes and comparisons at each time point, using a random-effects model⁵⁸. Then, a NMA will be performed within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons and accounting for correlations induced by multi-arm studies^{56, 59}. Both pairwise meta-analysis and NMA will be performed for children/adolescents and adults, respectively. The analysis will be performed using STATA v.13. (MRC Biostatistics Unit, Cambridge, UK, <http://cmimg.cochrane.org/network-meta-analysis-toolkit>); the codes and description of the methodology can be found in <http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis>⁶⁰⁻⁶². Studies in children and adolescents will be combined in the statistical analyses. For primary outcomes, we will also assess the quality of evidence using GRADE⁶³ (GRADE Working Group 2004)⁶³. The criteria considered are: study limitations, indirectness, inconsistency, imprecision, and reporting bias. We will assign four levels of quality of evidence: *high, moderate, low, and very low*.

Assessment of statistical heterogeneity

In standard pairwise meta-analyses, we will estimate different heterogeneity variances for each pairwise comparison. In network meta-analysis, we will assume a common estimate for the heterogeneity variance (τ^2) within and across comparisons. The presence of statistical heterogeneity within each pairwise comparison will be assessed by visual inspection of the

forest plots and by calculating the I-squared statistic and its confidence limits⁶⁴. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the common τ^2 estimated from the NMA models⁶⁵. For dichotomous outcomes, the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner et al.⁶⁶.

Assessment of statistical incoherence

Local and global approaches will be used to evaluate statistical incoherence. To evaluate the presence of incoherence locally, we will use the loop-specific approach⁶⁷. This method evaluates the incoherence assumption by calculating the incoherence factor as the difference between direct and indirect estimates for a specific comparison in each closed loop formed by the network of trials (using the Bucher method) and their relative 95% confidence intervals. The incoherence factor is the logarithm of the ratio of two risk ratios (RRR) from direct and indirect evidence in the loop. Then we will examine whether there are any material discrepancies; if the 95% CI does overlap with 1, the hypothesis of incoherence is not rejected, as described in Salanti⁶⁸. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using the 'ifplot' command in STATA. To check the assumption of consistency in the entire network, we will use the 'design-by-treatment' model⁶⁹. This method accounts for different source of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer the presence of inconsistency from any source in the entire network based on a chi-square test. The design-by-treatment model will be performed in STATA using the 'mvmeta' command. Inconsistency and heterogeneity are interweaved; to distinguish between these two sources of variability we will employ the I-squared for

inconsistency that measures the percentage of variability that cannot be attributed to random error or heterogeneity (within comparison variability) ⁶⁵.

Investigation of heterogeneity and inconsistency

In the case of important clinical or statistical inconsistency, the feasibility of multiple-treatments meta-regression or subgroup analysis will be considered to investigate the possible sources of heterogeneity and incoherence by using the following effect modifiers (for primary outcomes only):

1. studies sponsored vs. those not sponsored by pharmaceutical companies;
2. males vs. females;
3. children vs. adolescents, since some medications (e.g., SSRIs) have been reported to have different efficacy in children vs. adolescents ⁷⁰; [if study data are not available for children (aged < 12 years) and adolescents (aged ≥ 12) separately, they will only be included in the main analysis (i.e. combining children and adolescents together - see above: “Synthesis of results”)].

Sensitivity analyses

We will explore the feasibility of conducting the following sensitivity analyses by excluding:

- 1) studies where all participants have IQ < 70;
- 2) studies where all participants have psychiatric/neurologic comorbidities;
- 3) studies lasting less than 2 weeks;
- 4) studies for which imputation of missing data was required;
- 5) studies with overall high or unclear risk of bias;
- 6) cross-over trials;

7) studies including patients resistant to ADHD medication;

8) studies recruiting only non-treatment-naïve patients;

7) A final sensitivity analysis will address whether unbalanced doses affected the results. To exclude trials with non-equivalent comparisons, we will apply a previously validated approach used for antidepressant trials⁷¹. For this, we put together a roster (see Table 2 and 3) in which low and high doses of the drugs included in the present NMA are described. Table 2 is based on FDA indications. This roster will be employed to detect inequalities in dosing that could affect comparative efficacy by excluding trials with low doses of one drug and high doses of the other (or vice-versa). We will not consider starting doses if these were supposed to be increased during the trial.

ETHICS AND DISSEMINATION

No ethical issues are foreseen since ethical approval has been obtained for each study that will be included in the systematic review/meta-analysis. The results of this study will be published in a peer-reviewed journal and will be also possibly presented at national and international meetings of (child) psychiatry, psychology, and paediatrics.

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GUARANTOR OF THE REVIEW: Dr. Samuele Cortese

AUTHORS' CONTRIBUTION: Dr Cortese drafted the protocol (except the literature search and statistical analysis sections). Drs. Shokrane and Xia drafted the literature search section. Dr. Del Giovane drafted the statistical analysis section. All other co-authors critically reviewed the protocol and amended it.

COMPETING INTEREST STATEMENT

Dr. Cortese has received reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non profit organization, in relation to lectures that he delivered for ACAMH.

Dr. Mohr-Jensen has been a speaker for HB Pharma/Medice.

Dr. Carucci collaborated within projects from the European Union (7FP) and has received travel support from Shire Pharmaceutical Company; she collaborated as sub-investigator in sponsored clinical trial by Shire Pharmaceutical Company.

Dr. Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, Otsuka, PCM scientific, Shire and Viforpharma. He received conference support or speaker's fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press.

Dr. Zuddas has received honoraria for participating to Advisory board or Data Safety Monitory Boards from Eli Lilly, Otsuka, Lundbeck, Takeda and EduPharma. He has also received royalties from Oxford University Press and Giunti OS, and research grants from Lundbeck, Roche, Shire and Vifor.

Dr. Steinhausen has worked as an advisor and speaker for the following pharmaceutical companies: Janssen-Cilag, Eli Lilly, Novartis, Medice, Shire, and UCB and has also received unrestricted grants for postgraduate training courses or conferences and research by Janssen-Cilag, Eli Lilly, Novartis, Medice, and Swedish Orphan International. He receives book royalties from Cambridge University Press, Elsevier, Hogrefe, Huber, Klett, and Kohlhammer publishers.

Dr. Cipriani has served as an expert witness for a patent litigation case about quetiapine extended-release and is supported by the NIHR Oxford Cognitive Health Clinical Research Facility.

Dr. Coghill reports grants and personal fees from Shire, personal fees from Eli Lilly, grants from Vifor, personal fees from Novartis, personal fees from Oxford University Press.

Drs. Adamo, Hayes, Bhatti, Del Giovane, Atkinson, Simonoff, Barbui, Purgato, Shokraneh and **Xia** report no competing conflicts of interest.

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Table 1. Washout periods.

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

Table 2. Dose range of medication included in the network meta-analysis for children/adolescents, according to the FDA whenever possible (as retrieved in <https://dailymed.nlm.nih.gov/dailymed/> or <http://www.accessdata.fda.gov/>; other source: Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attention deficit/hyperactivity disorder: emerging concepts from new data. J Child Adolesc Psychopharmacol 2007;17:393-406)

Drug	Min. daily dose	Max. daily dose
Methylphenidate hydrochloride immediate release	10 mg	60 mg
Methylphenidate hydrochloride intermediate acting	20 mg	60 mg
Methylphenidate hydrochloride long acting	18 mg	54 mg (children) 72 mg (adolescents) (do not exceed 2 mg/Kg/day)
Methylphenidate hydrochloride oral solution	10 mg	60 mg
Methylphenidate hydrochloride chewable tablets	10 mg	60 mg
d,l-threo Methylphenidate slow release	20 mg	60 mg
Dexmethylphenidate (d-threo-methylphenidate) immediate release	5 mg	20 mg
Dexmethylphenidate (d-threo-methylphenidate) XR	5 mg (children)	20 mg
Dextro-amphetamine	2.5 mg (children 3-5 y)	Children 3-5 y: not specified

immediate release	5 mg (children ≥ 6 y)	Children ≥ 6 y: 40 mg
Dextro-amphetamine ER	10 mg (children 6-12 y and adolescents 13-17 y)	30 mg (children 6-12 y) Adolescents: not specified
Mixed Amphetamine Salts	2.5 mg (children 3-5 y) 5 mg (children ≥ 6 y)	40 mg (children ≥ 6 y)
Mixed Amphetamine Salts XR	10 mg (children ≥ 6 y) 10 mg, increased to 20 mg (adolescents 13-17 y)	30 mg (children ≥ 6 y) Adolescents 13-17 y and
Lisdexamfetamine	30 mg (individuals ≥ 6 y)	70 mg (individuals ≥ 6 y)
Atomoxetine	0.5 mg/Kg (children and adolescents ≤ 70 Kg) 40 mg (children and adolescents > 70 Kg and adults)	1.4 (1.8 in Europe) mg/Kg or 100 mg, whichever less (children and adolescents ≤ 70 Kg) 100 mg (children and adolescents > 70 Kg)
Clonidine immediate release	Children/adolescents < 45 Kg: 0.05 mg Children/adolescents > 45 Kg: 0.1 mg	Children/adolescents < 45 Kg: 0.2 mg Children/adolescents > 45 Kg: 0.4 mg
Clonidine extended release	0.1 mg	0.4 mg
Guanfacine immediate release	0.5 mg	N/S
Guanfacine extended release	1 mg	7 mg
Bupropion IR	N/S	N/S
Bupropion SR	N/S	N/S
Bupropion XL	N/S	N/S
Modafinil	200 mg	400 mg

Table 3. Dose range of medication included in the network meta-analysis for adults, according to the FDA whenever possible (as retrieved in <https://dailymed.nlm.nih.gov/dailymed/> or <http://www.accessdata.fda.gov/>; other sources: <http://integratedcare-nw.org/docs/PCPtraining/AdultADHDSummary-Recommendations.pdf>; Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attention deficit/hyperactivity disorder: emerging concepts from new data. *J Child Adolesc Psychopharmacol* 2007;17:393-406)

Drug	Min. daily dose	Max. daily dose
Methylphenidate hydrochloride immediate release	10 mg	60 mg
Methylphenidate hydrochloride intermediate acting	20 mg	60 mg
Methylphenidate hydrochloride long acting	18-36 mg	72 mg
Methylphenidate hydrochloride oral solution	10 mg	60 mg
Methylphenidate hydrochloride chewable tablets	10 mg	60 mg
d,l-threo Methylphenidate slow release	20 mg	60 mg
Dexmethylphenidate (d-threo-methylphenidate) immediate release	5 mg	20 mg
Dexmethylphenidate (d-threo-methylphenidate) XR	10 mg (adult)	20 mg
Dextro-amphetamine	N/S	N/S

immediate release		
Dextro-amphetamine ER	20 mg	N/S
Mixed Amphetamine Salts	N/S	N/S
Mixed Amphetamine Salts XR	20 mg	N/S
Lisdexamfetamine	30 mg	70 mg
Atomoxetine	N/S	100 mg
Clonidine immediate release	N/S	N/S
Clonidine extended release	0.1 mg	0.4 mg
Guanfacine immediate release	0.5 mg	N/S
Guanfacine extended release	1 mg	7 mg
Bupropion IR	100 mg bid	100 mg tid
Bupropion SR	150 mg qam	150 mg bid
Bupropion XL	150 mg qam	300 mg qam
Modafinil	200 mg	400 mg

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review: Pag. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Pag. 5 and 8
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Pag. 1-3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review. Pag. 24
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review Pag. 24
Sponsor	5b	Provide name for the review funder and/or sponsor Pag. 24
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Pag. 24
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Pag.6-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Pag. 8
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 Pag.8-13
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 Pag. 13-17
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 Pag. 15
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Pag. 16-18

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) Pag. 16-17
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 Pag. 17-18
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 Pag. 17-18
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Pag. 12-13
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 Pag. 18-19
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Pag. 21
	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) Pag. 21-23
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Pag. 23-24
	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) Pag. 23
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Pag. 21

*** 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.**

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