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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 We will also search for unpublished studies using international clinical trial registries and contacting relevant drug companies.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, dexmethylphenidate, amphetamine derivatives (including 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

Strengths and limitations of this study

- This is the first comprehensive network meta-analysis (NMA) addressing the efficacy and tolerability of medications for attention-deficit/hyperactivity disorder (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 efficacy and acceptability.
- Subgroup and sensitivity analyses will address important clinical questions (eg, differences between sexes, comparison between children and adolescents, and subgroup analysis in participants without neurological/psychiatric comorbidities).
- The findings of this NMA have the potential to inform and influence clinical decision-making and guideline development.
- 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.

peer-reviewed journal and possibly presented at relevant national and international conferences.

Trial registration number: CRD42014008976.

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 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 USA[9] and are substantial in other countries as well.[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,[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 (eg, methylphenidate and amphetamine derivatives) and non-psychostimulant drugs (eg, atomoxetine, clonidine and guanfacine, among others). A large body of evidence from double-blind randomised controlled trials (RCTs), summarised in several meta-analyses in children, adolescents and/or adults, demonstrated that different classes of psychostimulants (eg, methylphenidate[15–18] or mixed amphetamine salts[19] and other amphetamine derivatives[20]) and some non-psychostimulant treatments, such as atomoxetine,[21–24] 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[27] or different classes and agents.[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 with other drugs.[31–33]

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 versus 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 synthesising information from a network of trials that have addressed the same question using different interventions.[36] An NMA relies on the combination of direct and indirect evidence, which can increase precision while randomisation is preserved.[37–41] Therefore, compared with 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]

While 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 the best of 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 an NMA (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 healthcare interventions.[47] 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 inpatients 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 socioeconomic 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 (eg, antiepileptic drugs for epilepsy or mood stabilisers 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 participants 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 washout periods for each individual drug); (5) studies including (a) participants 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) participants who were responders or stabilised/optimised to an ADHD medication (where stabilised/optimised means responders) during a run-in/open-label phase before of randomisation (irrespective of wash out period); (6) studies in which all included participants were deemed to be 'resistant' to a previous ADHD drug, as this would violate the transitivity assumption of NMA.[36]; and (7) Data from the withdrawal phase of a trial, in which already treated participants are randomised to either continue medication or switch to placebo, following an open-label phase.

Table 1 Washout periods

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

Types of interventions

We will include studies assessing any of the following drugs, as oral monotherapy (tablets, capsules, chewable compounds or liquid formulations), compared with each other or with placebo: methylphenidate, dexmethylphenidate, atomoxetine, amphetamine derivatives (including 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. 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,[25] and other meta-analyses have excluded

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 *et al*[72])

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 years) 5 mg (children ≥6 years)	Children 3–5 years: not specified Children ≥ 6-years: 40 mg
Dextro-amphetamine ER	10 mg (children 6–12 years and adolescents 13–17 years)	30 mg (children 6–12 years) Adolescents: not specified
Mixed amphetamine salts	2.5 mg (children 3–5 years) 5 mg (children ≥6 years)	40 mg (children ≥6 years)
Mixed amphetamine salts XR	10 mg (children ≥6 years) 10 mg, increased to 20 mg (adolescents 13–17 years)	30 mg (children ≥6 years) Adolescents 13–17 years and
Lisdexamfetamine	30 mg (individuals ≥6 years)	70 mg (individuals ≥ 6 years)
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
Buproprion SR	N/S	N/S
Bupropion XL	N/S	N/S
Modafinil	200 mg	400 mg

studies lasting <3 weeks,[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 ∼1 week of treatment and, to the best of 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 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.

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 *et al*[72])

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 two times a day	100 mg tid
Buproprion SR	150 mg qam	150 mg two times a day
Bupropion XL	150 mg qam	300 mg qam
Modafinil	200 mg	400 mg

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 precrossover phase, whenever this is reported in the paper. When data for the precrossover phase are not reported, we will contact study authors to gather them. If precrossover data are not reported and not available on request, we will use data at the end point (after crossing over), derived from appropriate statistical methods (ie, paired t-test),[49] only if there was a washout period (see table 1) between the two phases (precrossover and postcrossover) 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 intraclass 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 SDs will remain unchanged.

Exclusion criteria

Quasi-RCTs, 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, ie, inattentive plus hyperactive/impulsive symptoms), measured as end point 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 subscales of ADHD measures (ie, 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 end point scores are not reported but change scores are, we will use the

latter scores.[52] 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 mm Hg;
- Change in body weight, measured in kg.

Search strategy

We will search for 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 and 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. http://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 hyperactiv*(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 (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 comorbid (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 reference.[50] 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 judgement 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 (eg, 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 standardised mean difference (SMD) Hedges's adjusted g.[50] Dichotomous outcomes will be analysed by calculating the OR. Results from the NMA will be presented as summary relative effect sizes (SMD or OR) and relative 95% CIs 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. Separate analyses will be conducted considering lisdexamfetamine as part of amphetamine derivatives and as an individual drug. As described in Salanti *et al*,[53] 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 randomisation 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, CIs or SEs.[54] If these values are missing, attempts will be made to obtain SD or p values, t-values, CIs or SEs from trial authors. Where SDs are not available, a validated method for imputation will be used.[55] 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 synthesised 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 results.[50] 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 characteristics.[50]

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 transitivity:[56]

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 intransitivity.[57]

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 model.[58] Then, an NMA will be performed within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons and accounting for correlations induced by multiarm studies.[56 59] The 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 GRADE[63] (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 NMA, 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^2 statistic and its confidence limits.[64] The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the common τ^2 estimated from the NMA models.[65] 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 approach.[67] 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% CIs. The incoherence factor is the logarithm of the ratio of two risk ratios 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 Salanti *et al*.[68] 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' model.[69] 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 χ^2 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^2 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 versus those not sponsored by pharmaceutical companies;
2. males versus females;
3. children versus adolescents, since some medications (eg, SSRIs) have been reported to have different efficacy in children versus 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 (ie, combining children and adolescents together—see the Synthesis of results section)).

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/neurological comorbidities;
3. studies lasting <2 weeks;
4. studies for which imputation of missing data was required;
5. studies with overall high or unclear risk of bias;
6. crossover trials;
7. studies including patients resistant to ADHD medication;
8. studies recruiting only non-treatment-naïve patients;

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.[71] For this, we put together a roster (see tables 2 and 3) in which low and high doses of the drugs included in the present NMA are described. Tables 2 and 3 are 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.

DISSEMINATION

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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Contributors SC drafted the protocol (except the literature search and statistical analysis sections). FS and JX drafted the literature search section. CDG drafted the statistical analysis section. All other coauthors critically reviewed the protocol and amended it.

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REFERENCES

1. Polanczyk GV, Willcutt EG, Salum GA, *et al*. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol* 2014;43:434–42.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, fifth edition, DSM-5*. American Psychiatric Publishing, 2013.
3. World Health Organization (WHO). The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines 1992; diagnostic criteria for research 1993. Geneva: World Health Organization, 1992.
4. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005;366:237–48.
5. Cortese S, Holtmann M, Banaschewski T, *et al*. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry* 2013;54:227–46.
6. Polanczyk G, de Lima MS, Horta BL, *et al*. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007;164:942–8.
7. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006;36:159–65.
8. Simon V, Czobor P, Balint S, *et al*. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009;194:204–11.
9. Doshi JA, Hodgkins P, Kahle J, *et al*. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry* 2012;51:990–1002.
10. Holden SE, Jenkins-Jones S, Poole CD, *et al*. The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010). *Child Adolesc Psychiatry Ment Health* 2013;7:34.
11. Le HH, Hodgkins P, Postma MJ, *et al*. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. *Eur Child Adolesc Psychiatry* 2014;23:587–98.
12. Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:894–921.
13. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder CG72. 2008. http://www.nice.org.uk/CG72
14. Taylor E, Dopfner M, Sergeant J, *et al*. European clinical guidelines for hyperkinetic disorder—first upgrade. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 1):I7–30.
15. Castells X, Ramos-Quiroga JA, Rigau D, *et al*. Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: a meta-regression analysis. *CNS Drugs* 2011;25:157–69.
16. Koesters M, Becker T, Kilian R, *et al*. Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. *J Psychopharmacol (Oxford)* 2009;23:733–44.
17. Schachter HM, Pham B, King J, *et al*. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ* 2001;165:1475–88.
18. Van der Oord S, Prins PJ, Oosterlaan J, *et al*. Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. *Clin Psychol Rev* 2008;28:783–800.
19. Faraone SV, Biederman J. Efficacy of Adderall for attention-deficit/hyperactivity disorder: a meta-analysis. *J Atten Disord* 2002;6:69–75.
20. Castells X, Ramos-Quiroga JA, Bosch R, *et al*. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. *Cochrane Database Syst Rev* 2011;(6):CD007813.
21. Cheng JY, Chen RY, Ko JS, *et al*. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. *Psychopharmacology (Berl)* 2007;194:197–209.
22. Cunill R, Castells X, Tobias A, *et al*. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. *Pharmacoepidemiol Drug Saf* 2013;22:961–9.

23. Kratochvil CJ, Milton DR, Vaughan BS, *et al*. Acute atomoxetine treatment of younger and older children with ADHD: a meta-analysis of tolerability and efficacy. *Child Adolesc Psychiatry Ment Health* 2008;2:25.
24. Tanaka Y, Rohde LA, Jin L, *et al*. A meta-analysis of the consistency of atomoxetine treatment effects in pediatric patients with attention-deficit/hyperactivity disorder from 15 clinical trials across four geographic regions. *J Child Adolesc Psychopharmacol* 2013;23:262–70.
25. Storebo OJ, Ramstad E, Krogh HB, *et al*. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev* 2015;(11):CD009885.
26. Punja S, Shamseer L, Hartling L, *et al*. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev* 2016;(2):CD009996.
27. Coghill D, Banaschewski T, Zuddas A, *et al*. Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies. *BMC Psychiatry* 2013;13:237.
28. Faraone SV, Biederman J, Spencer TJ, *et al*. Comparing the efficacy of medications for ADHD using meta-analysis. *MedGenMed* 2006;8:4.
29. Bushe CJ, Savill NC. Systematic review of atomoxetine data in childhood and adolescent attention-deficit hyperactivity disorder 2009–2011: focus on clinical efficacy and safety. *J Psychopharmacol (Oxford)* 2014;28:204–11.
30. Hazell PL, Kohn MR, Dickson R, *et al*. Core ADHD symptom improvement with atomoxetine versus methylphenidate: a direct comparison meta-analysis. *J Atten Disord* 2011;15:674–83.
31. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry* 2010;71:754–63.
32. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry* 2011;11:176.
33. Peterson K, McDonagh MS, Fu R. Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. *Psychopharmacology (Berl)* 2008;197:1–11.
34. Taylor E. Uses and misuses of treatments for ADHD. The second Birgit Olsson lecture. *Nord J Psychiatry* 2014;68:236–42.
35. Sonuga-Barke EJ, Brandeis D, Cortese S, *et al*. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013;170:275–89.
36. Mavridis D, Giannatsi M, Cipriani A, *et al*. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health* 2015;18:40–6.
37. Hasselblad V. Meta-analysis of multitreatment studies. *Med Decis Making* 1998;18:37–43.
38. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Stat Med* 1996;15:2733–49.
39. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002;21:2313–24.
40. Salanti G, Kavvoura FK, Ioannidis JP. Exploring the geometry of treatment networks. *Ann Intern Med* 2008;148:544–53.
41. Cipriani A, Higgins JP, Geddes JR, *et al*. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013;159:130–7.
42. Cipriani A, Zhou X, Del *et al*. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881–90.
43. Catala-Lopez F, Hutton B, Nunez-Beltran A, *et al*. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: protocol for a systematic review and network meta-analysis of randomized controlled trials. *Syst Rev* 2015;4:19.
44. Roskell NS, Setyawan J, Zimovetz EA, *et al*. Systematic evidence synthesis of treatments for ADHD in children and adolescents: indirect treatment comparisons of lisdexamfetamine with methylphenidate and atomoxetine. *Curr Med Res Opin* 2014;30:1673–85.
45. Li Y, Gao J, He S, *et al*. An evaluation on the efficacy and safety of treatments for attention deficit hyperactivity disorder in children and adolescents: a comparison of multiple treatments. *Mol Neurobiol* 2016.
46. Bushe C, Day K, Reed V, *et al*. A network meta-analysis of atomoxetine and osmotic release oral system methylphenidate in the treatment of attention-deficit/hyperactivity disorder in adult patients. *J Psychopharmacol (Oxford)* 2016;30:444–58.
47. Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
48. Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III: The issue of carry-over. *Stat Med* 2002;21:2161–73.
49. Elbourne DR, Altman DG, Higgins JP, *et al*. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;31:140–9.
50. Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions*, version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org
51. Ukoumunne OC, Gulliford MC, Chinn S, *et al*. Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review. *Health Technol Assess* 1999;3:iii–92.
52. da Costa BR, Nuesch E, Rutjes AW, *et al*. Combining follow-up and change data is valid in meta-analyses of continuous outcomes: a meta-epidemiological study. *J Clin Epidemiol* 2013;66:847–55.
53. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
54. Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;313:1200.
55. Furukawa TA, Barbui C, Cipriani A, *et al*. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7–10.
56. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80–97.
57. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med* 2013;11:159.
58. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
59. Miladinovic B, Hozo I, Chaimani A, *et al*. Indirect treatment comparison. *Stata J* 2014;14:76–86.
60. Chaimani A, Higgins JP, Mavridis D, *et al*. Graphical tools for network meta-analysis in STATA. *PLoS ONE* 2013;8:e76654.
61. White IR. Multivariate random-effects meta-regression: updates to mvmeta. *Stata J* 2011;11:255–70.
62. White IR, Barrett JK, Jackson D, *et al*. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3:111–25.
63. Salanti G, Del GC, Chaimani A, *et al*. Evaluating the quality of evidence from a network meta-analysis. *PLoS ONE* 2014;9:e99682.
64. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
65. Jackson D, Barrett JK, Rice S, *et al*. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Stat Med* 2014;33:3639–54.
66. Turner RM, Davey J, Clarke MJ, *et al*. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41:818–27.
67. Veroniki AA, Vasiliadis HS, Higgins JP, *et al*. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42:332–45.
68. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;62:857–64.
69. Higgins JP, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
70. Mayes TL, Tao R, Rintelmann JW, *et al*. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? *CNS Spectr* 2007;12:147–54.
71. Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746–58.
72. 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.