BMJ Open

Comparative cardiovascular side effects of medications for attention-deficit/hyperactivity disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis

Alice Lannes,[1,2,3] Luis C Farhat,[4] Cinzia Del Giovane,[5,6] Andrea Cipriani ,[7,8] Alexis Revet ,[1,2] Samuele Cortese[9,10,11,12,13]

To cite: Lannes A, Farhat LC, Del Giovane C, *et al*. Comparative cardiovascular side effects of medications for attention-deficit/hyperactivity disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis. *BMJ Open* 2022;**12**:e062748. doi:10.1136/bmjopen-2022-062748

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062748).

AR and SC contributed equally.

Received 10 March 2022
Accepted 13 September 2022

For numbered affiliations see end of article.

Correspondence to
Dr Alexis Revet;
revet.a@chu-toulouse.fr

ABSTRACT

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

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OpenGrey, Web of Science) from their inception and contact study authors/drug manufacturers to gather relevant unpublished information.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

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

PROSPERO registration number CRD42021295352.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterised by persistent and impairing inattention and/or hyperactivity/impulsivity that are inappropriate for the developmental level and hinder daily functions.[1] ADHD is the most commonly diagnosed neurodevelopmental disorder, with an estimated worldwide prevalence around 5%–7% in school age children[2 3] and 2.5% in adults.[4] Impairing symptoms of ADHD persist in adulthood in around 75% of the cases.[5 6] Several studies across countries[7 8] have highlighted the substantial economic impact of ADHD. The treatment of people with ADHD includes non-pharmacological and pharmacological strategies. Drugs approved by the US Food and Drug Administration (FDA) include stimulants (amphetamines and methylphenidate) and non-stimulants

(atomoxetine, clonidine, guanfacine extended release and viloxazine). Medications for ADHD have been found to be efficacious, effective and generally well tolerated, although their use may be associated with undesirable adverse events.[9 10]

Although treatment-related adverse events can generally be managed, safety may be a concern for some patients, particularly those with pre-existing cardiovascular conditions[11] because there is some evidence that ADHD medications may impact the cardiovascular system. Indeed, a meta-analysis of randomised controlled trials (RCTs) of stimulants in adults[12] found a mean increase in heart rate of 5.7 beats/min and a mean increase in systolic blood pressure of 2.0 mm Hg, while abnormal ECG changes were observed in less than 2% of participants. Vitiello *et al* examined the association of stimulant medications with blood pressure and heart rate over 10 years.[13] Even though no significant overall increase in the risk of hypertension over the period was found, stimulants had a persistent adrenergic effect on heart rate during treatment, with greater cumulative stimulant exposure being associated with a higher heart rate at years 3 and 8 of the 10-year follow-up period. Liang *et al* conducted a pairwise meta-analysis on the effects of methylphenidate and atomoxetine on heart rate and systolic blood pressure.[14] They found that children/adolescents and adults treated with methylphenidate had significant increases in heart rate and systolic blood pressure (post-treatment vs pre-treatment) compared with placebo, and that children and adolescents treated with atomoxetine had significant increases in the same outcomes compared with those treated with methylphenidate. However, whether these cardiovascular changes associated with stimulants translate to cardiovascular-related morbidity–mortality is unclear as highlighted by a recent meta-analysis[15] which found no significant association between pharmacological treatment of ADHD and sudden death, stroke, myocardial infarction or death from any cause (although only eight studies were included and some estimates were relatively imprecise with some of the CIs failing to exclude important harm, in particular for sudden death/arrhythmia).

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

MATERIALS AND METHODS

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

Selection criteria

Population

Inclusion criteria

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

Exclusion criteria

We will exclude studies that recruited participants with:

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

Table 1 Washout periods

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

Interventions and exposures

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

Outcomes

We will focus on the three following outcomes:

1. Change in blood pressure (diastolic and systolic blood pressure), measured in mm Hg.
2. Change in heart rate, measured in beats/min.
3. Change in any reported ECG parameters.

Timing of outcome assessment

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

Type of studies

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

Search strategy

Electronic searches

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

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

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

(“Attention Deficit Disorder with Hyperactivity”[Mesh] OR adhd[tiab] OR hkd[tiab] OR addh[tiab] OR hyperkine*[tiab] OR “attention deficit*”[tiab] OR hyper-activ*[tiab] OR hyperactiv*[tiab] OR overactive[tiab] OR inattentive[tiab] OR impulsiv*[tiab]) AND (“Amphetamines”[Mesh] OR “Bupropion”[Mesh] OR “Clonidine”[Mesh] OR “Methylphenidate”[Mesh] OR “Dexmethylphenidate”[Mesh] OR “Guanfacine”[Mesh] OR Adderall[tiab] OR Amphetamine[tiab] OR Desoxyn*[tiab] OR Phenopromin[tiab] OR Amfetamine[tiab] OR Phenamine[tiab] OR Centramina[tiab] OR Fenamine[tiab] OR Levoamphetamine[tiab] OR Dexamfetamine[tiab] OR Dexamphetamine[tiab] OR Dexedrine[tiab] OR Dextroamphetamine[tiab] OR DextroStat[tiab] OR Oxydess[tiab] OR Methylamphetamine[tiab] OR Methylenedioxyamphetamine[tiab] OR Methamphetamine[tiab] OR Chloroamphetamine[tiab] OR Metamfetamine[tiab] OR Deoxyephedrine[tiab] OR Desoxyephedrine[tiab] OR Ecstasy[tiab] OR Atomoxetine[tiab] OR Biphentin[tiab] OR Bupropion[tiab] OR Amfebutamone[tiab] OR Zyntabac[tiab] OR Quomen[tiab] OR Wellbutrin[tiab] OR Zyban[tiab] OR Catapres*[tiab] OR Clonidine[tiab] OR Klofenil[tiab] OR Clofenil[tiab] OR Chlophazolin[tiab] OR Gemiton[tiab] OR Hemiton[tiab] OR Isoglaucon[tiab] OR Klofelin[tiab] OR Clopheline[tiab] OR Clofelin[tiab] OR Dixarit[tiab] OR Concerta[tiab] OR Daytrana[tiab] OR Methylphenidate[tiab] OR Equasym[tiab] OR Methylin[tiab] OR Tsentedrin[tiab] OR Centedrin[tiab] OR

Phenidylate[tiab] OR Ritalin*[tiab] OR Duraclon[tiab] OR Elvanse[tiab] OR Focalin[tiab] OR Dexmethylphenidate[tiab] OR Guanfacine[tiab] OR Estulic[tiab] OR Tenex[tiab] OR Kapvay[tiab] OR Lisdexamfetamine[tiab] OR Vyvanse[tiab] OR Medikinet[tiab] OR Metadate[tiab] OR Modafinil[tiab] OR Nexiclon[tiab] OR Quillivant[tiab] OR Strattera[tiab] OR Viloxazine[tiab] OR Qelbree[tiab] OR Vivalan[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh]).

Other sources

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

Selection of studies

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

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

Data extraction

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

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

Assessment of study quality and risk of bias

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

Data analysis

Synthesis of results and measure of treatment effect

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

Statistical analysis

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

To assess transitivity assumption, we will compare the distribution of clinical and methodological variables that

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

The Confidence In Network Meta-Analysis software will be used to assess the confidence of evidence contributing to each network estimate.[27] This tool is based on a methodological framework which shows how much information each study contributes to the results from NMA by considering six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence.

Additional analyses

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

Patient and public involvement

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

ETHICS AND DISSEMINATION

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

REGISTRATION OF THE PROTOCOL, TIMELINE OF THE STUDY AND PLANNED CONTRIBUTIONS TO THE META-ANALYSIS

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

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

Author affiliations
[1]CERPOP/UMR1295, Inserm, UPS, University of Toulouse 3, Toulouse, France
[2]Department of Child and Adolescent Psychiatry, University Hospital Centre Toulouse, Toulouse, France
[3]Adolescent Hospitalization Unit, Department of Child and Adolescent Psychiatry, Lannemezan Hospital, Lannemezan, France
[4]Department of Psychiatry, Faculdade de Medicina FMUSP, Universidade de São Paulo, Sao Paulo, Brazil
[5]Institute of Primary Health Care, University of Bern, Bern, Switzerland
[6]Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, Modena, Italy
[7]Department of Psychiatry, University of Oxford, Oxford, UK
[8]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK
[9]School of Psychology, Centre for Innovation in Mental Health (CIMH), Faculty of Environmental and Life Sciences, University of Southampton, Highfield Campus, Southampton, UK
[10]Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK
[11]Solent NHS Trust, Southampton, UK
[12]Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, New York, USA
[13]Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK

Twitter Andrea Cipriani @And_Cipriani

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

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SC declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP) and from

Healthcare Convention for educational activity on ADHD. LCF receives scholarship support from grant #2021/08540-0, São Paulo Research Foundation (FAPES). AC is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017-08-ST2-006), by the NIHR Oxford and Thames Valley Applied Research Collaboration and by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005); has received research, educational and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR or the UK Department of Health.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Andrea Cipriani http://orcid.org/0000-0001-5179-8321
Alexis Revet http://orcid.org/0000-0002-8051-1657

REFERENCES

1 Feldman HM, Reiff MI. Clinical practice. attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med* 2014;370:838–46.
2 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.
3 Thomas R, Sanders S, Doust J, *et al*. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 2015;135:e994–1001.
4 Simon V, Czobor P, Bálint S, *et al*. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009;194:204–11.
5 Sibley MH, Mitchell JT, Becker SP. Method of adult diagnosis influences estimated persistence of childhood ADHD: a systematic review of longitudinal studies. *Lancet Psychiatry* 2016;3:1157–65.
6 Sibley MH, Arnold LE, Swanson JM, *et al*. Variable patterns of remission from ADHD in the multimodal treatment study of ADHD. *Am J Psychiatry* 2022;179:142–51.
7 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.
8 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.
9 Cortese S. Pharmacologic treatment of attention deficit-hyperactivity disorder. *N Engl J Med* 2020;383:1050–6.
10 Zhang L, Lagerberg T, Chen Q, *et al*. Prediction of treatment dosage and duration from free-text prescriptions: an application to ADHD medications in the Swedish prescribed drug register. *Evid Based Ment Health* 2021;24:146–52.
11 Montastruc F, Montastruc G, *et al*, medical pharmacologist. Cardiovascular safety of methylphenidate should also be considered in adults. *BMJ* 2016;353:i3418.
12 Mick E, McManus DD, Goldberg RJ. Meta-analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. *Eur Neuropsychopharmacol* 2013;23:534–41.
13 Vitiello B, Elliott GR, Swanson JM, *et al*. Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. *Am J Psychiatry* 2012;169:167–77.
14 Liang EF, Lim SZ, Tam WW, *et al*. The effect of methylphenidate and atomoxetine on heart rate and systolic blood pressure in young people and adults with attention-deficit hyperactivity disorder (ADHD): systematic review, meta-analysis, and meta-regression. *Int J Environ Res Public Health* 2018;15:E1789.
15 Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. *Eur Child Adolesc Psychiatry* 2019;28:1283–93.
16 Cortese S, Adamo N, Del Giovane C, *et al*. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018;5:727–38.
17 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
18 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
19 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
20 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.
21 Cortese S, Adamo N, Mohr-Jensen C, *et al*. 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. *BMJ Open* 2017;7:e013967.
22 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
23 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.
24 Higgins JPT, 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.
25 Veroniki AA, Vasiliadis HS, Higgins JPT, *et al*. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42:332–45.
26 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
27 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. Cinema: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.