Systematic Reviews

PROTOCOL

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Efficacy of pharmacological interventions for ADHD: protocol for an updated systematic review and dose–response network meta-analysis

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Abstract

Background Attention-deficit/hyperactivity disorder (ADHD) affects approximately 5% of children globally, with symptoms often persisting into adulthood. While pharmacological interventions are commonly employed for management, understanding the optimal dosing for efficacy and tolerability remains crucial. This study aims to conduct a dose–response network meta-analysis to estimate the efficacy of pharmacological treatments across different doses, aiming to inform clinical decision-making and improve treatment outcomes.

Methods This updated systematic review will include randomized controlled trials evaluating ADHD medication efficacy in children, adolescents, and adults. An updated search from a 2018 NMA will be conducted across multiple electronic databases with no language restrictions, using specific eligibility criteria focused on randomized controlled trials. The primary outcome will assess the severity of ADHD core symptoms, while secondary outcomes will consider treatment tolerability. A dose–response Bayesian hierarchical model will be used to estimate dose–response curves for each medication, identifying optimal dosing strategies.

Discussion With this dose–response network meta-analysis, we aim to better understand the dose–response relationship of pharmacological treatment in ADHD, which could help clinician to the identification of optimal doses.

Systematic review registration OSF https://doi.org/10.17605/OSF.IO/3MY4A.

Keywords Dose-responsenetwork meta-analysis, Attention deficit/hyperactivity disorder, Pharmacotherapy

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Background

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5-TR) [1]. It is a common condition, affecting around 5% of children globally [2]. Impairing symptoms of ADHD persist into adulthood in 40 to 60% of cases [3], resulting in an overall adult ADHD prevalence of approximately 3% [2]. When left untreated, ADHD can lead to significant challenges in academic, familial, and social domains [4].

The management of ADHD involves psychological and/or pharmacological interventions. Pharmacological options include psychostimulants such as methylphenidate and amphetamine derivatives, as well as non-stimulant medications like atomoxetine, clonidine, guanfacine, and viloxazine. Evidence in the comparative efficacy and tolerability of these medications is crucial to inform clinical decision-making.

Network meta-analysis (NMA) is a statistical method for comparing treatments, utilizing all available evidence [5, 6]. This approach enables indirect estimates for treatment comparisons that were not tested in randomized controlled trials (RCTs), thus helping to fill in gaps in our knowledge of relative treatment efficacy.

In 2018, Cortese and colleagues published a NMA of 133 double-blind RCT [7]. For ADHD core symptoms rated by clinicians, in children and adolescents with a time frame around 12 weeks, all included drugs were found to be superior to placebo. In adults, there was evidence that amphetamines, methylphenidate, bupropion, and atomoxetine were better than placebo, but not modafinil. With respect to tolerability, amphetamines were inferior to placebo in both children and adolescents and adults. In head-to-head comparisons, only differences in efficacy (clinicians' ratings) were found, favoring amphetamines over modafinil, atomoxetine, and methylphenidate in both children and adolescents and adults. While results from this NMA can inform clinical guidelines, it is important to note that this analysis did not account for the dosage. Information on dosage, however, is crucial when considering the efficacy of a medication. Evidence on the efficacy of different doses of medication is particularly relevant in the light of research indicating that children and adolescents in the community often receive small doses of stimulants on a daily basis [8–11]. This can decrease both the efficacy of and adherence to treatment [10, 12].

Dose–effect network meta-analysis (DE-NMA) is an extension of the basic NMA model, which explicitly models the dose–response relationship when comparing different treatments [13, 14]. Including dosage information in NMA allows for the exploration of dose–response relationships in a consistent way. Understanding the dose–response relationship not only contributes to a more comprehensive understanding of treatment effects but also facilitates the identification of optimal doses, i.e., doses that strike a balance between maximizing treatment benefits and minimizing harms. This information is crucial for guiding clinicians in identifying and recommending optimal doses for improved therapeutic outcomes.

This study outlines a DE-NMA protocol for ADHD medications; to the best of our knowledge, this is the first such study in the field.

The primary objectives include estimating dose–response curves for efficacy and acceptability in children/adolescents and adults separately. The study also aims to identify clinically significant efficacy doses, categorized by pharmacological class, and present the dose–response relationship in comparison to placebo.

Methods

This protocol has been preregistered on OSF at https://doi.org/https://doi.org/10.17605/OSF.IO/3MY4A. This protocol follows the PRISMA-P guidelines. The PRISMA-P checklist can be found in Appendix Table S1.

Search strategy

We will update the search for RCTs of medications for ADHD from the NMA [7] published in 2018 (last search April 7, 2017), using the same search strategy and syntax, with the addition of a medication, viloxazine, approved by the US Food and Drug Administration (FDA) for ADHD in 2021. We will search the following electronic databases: PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations and Theses (UK and Ireland), ProQuest Dissertations and Theses (abstracts and international), and the WHO International Trials Registry Platform, including ClinicalTrials.gov. We will also search the FDA, European Medicines Agency, and relevant drug manufacturers' websites, and we will check relevant 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. No language restrictions will be applied.

We will use search terms related to ADHD combined with a list of terms for ADHD medications. The search strategy will be adapted for each database (see Appendix).

Selection criteria

Study design

We will include double-blinded RCTs (parallel-group or crossover trials). In crossover studies, we will only use the first intervention phase to avoid carry-over effects. When data for the pre-crossover phase are not reported, we will contact study authors to gather them. If these data are not available, we will use data at the endpoint (after crossing over), derived from appropriate statistical methods (i.e., paired *t*-test), only if there was a washout period (see Appendix Table S2) between the two phases (pre-crossover and post-crossover) of the trial. Quasi-RCTs, open-label or single-blind RCTs, and N-of-1 trials will be excluded.

Population

We will include studies recruiting participants with the following characteristics:

(1) Age ≥ 5 years (children, adolescents, and adults)
(2) Inpatients or outpatients
(3) Meeting the DSM-III, III-R, IV, IV-TR, or V criteria for a primary diagnosis of ADHD, ICD-10 criteria for a primary diagnosis of hyperkinetic disorder (HKD), or ICD-11 criteria for ADHD.

We will not impose any restriction on ADHD subtype/presentation, gender, IQ, or socioeconomic status of participants. Concerning neuropsychiatric 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.

We will exclude studies with following characteristics:

(1) Recruiting participants with a diagnosis of minimal brain dysfunction, which would not be comparable with DSM definitions of ADHD or ICD definitions of HKD
(2) In which ADHD is a comorbid disorder secondary to a genetic syndrome
(3) Enrolling participants defined as "hyperkinetic" or "hyperactive" without application of standardized diagnostic criteria or using DSM-II criteria as they did not use standardized criteria for ADHD diagnosis
(4) Recruiting patients who were taking ADHD medication prior to entering the study, unless participants completed an appropriate washout period before starting the study trial (see Appendix Table S2)
(5) Including (a) participants who previously responded (according to the definition provided in the study) to the same medication tested in the randomized phase (irrespective of washout period) or (b) participants who were responders or stabilized/optimized to an ADHD medication during a run-in phase before of randomization (irrespective of wash out period)
(6) In which all included participants were deemed to be "resistant" to a previous ADHD drug
(7) Data from the withdrawal phase of a trial, in which already treated participants are randomized to either continue medication or switch to placebo, following an open-label phase.

Treatment

We will include studies assessing any of the following drugs, as oral monotherapy:

(1) Methylphenidate, dexmethylphenidate, atomoxetine, AMP derivatives (including lisdexamfetamine), clonidine, guanfacine, bupropion, modafinil, and viloxazine
(2) For at least seven consecutive days since response to adequate doses of psychostimulants can be appreciated already after approximately 1 week of treatment
(3) All dose levels, including unlicensed doses, will be included.

We will exclude pharmacological treatment combined with psychotherapy (other than psychoeducation).

Comparators (control)

Comparator included will be (1) placebo or (2) any medication among the list above.

Outcomes

- Primary outcome (efficacy): Continuous severity of ADHD core symptoms (total combined, i.e., inattentive plus hyperactive/impulsive symptoms), measured as endpoint score on a standardized scale filled out by parents, teachers, patients, or clinician(s). We will run separate analyses for each type of raters (i.e., parents, teacher, patients, clinician). Where there are ratings based on two or more scales, only one scale will be included data from in the analysis. The choice of scale to include will be made in the following order: ADHD rating scale (total score), SNAP ADHD (total score), Conners rating scale (any version, ADHD total score), or other ADHD scales.

- Secondary outcomes: Tolerability of treatment, defined as the proportion of patients who left the study due to any side effects

Data collection

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."

As a first step, two authors will screen the titles and abstracts of all non-duplicated papers and determine the relevance of each paper. They will agree on a final list, with any discrepancies resolved by consensus. If consensus cannot be reached, a third senior author will act as an arbitrator. If there is any uncertainty about the inclusion of a paper, it will proceed to the next stage of the screening process.

Then, the articles that pass stage 1 screening will be downloaded and evaluated for eligibility by two authors, separately. Any differences in opinion will be resolved through mutual agreement between the two authors, and if necessary, a third senior author will act as an arbitrator. Data from multiple reports of the same study will be combined. In case of need, we will contact the corresponding author to clarify the eligibility of the study.

The following data will be collected from each included study:

- Study citation, year(s) of study, year of publication, location, setting, number of centers, design (type of RCT), sample size, diagnostic criteria, and funding/sponsor (industry or academic)
- Characteristics of study participants (with position and dispersion parameters), including gender, age, the presence and type of comorbid (neuro)psychiatric conditions, IQ scores, and number of patients with ADHD medications naive at baseline or previously exposed to other ADHD medications
- Characteristics of interventions: Doses, formulation, and add-on interventions
- Outcomes: Mean, standard deviation, number of events, and times of measurement

Risk-of-*bias* assessment

Two reviewers will independently assess the risk of bias of retained RCTs using the Cochrane risk-of-bias tool version 2 (RoB 2.0) [15]. We will assess the risk of bias in respect of our primary outcome. In case of disagreement between the two reviewers, we will discuss it with a third, senior reviewer.

Data analysis

We will perform a DE-NMA independently for children/adolescents (< 18 years) and adult (≥ 18 years), adolescents (≥ 12; < 18), and for children (≥ 5; < 12).

Treatment nodes and class agents

(1) Methylphenidate immediate release (IR) or extended release (XR): Dexmethylphenidate IR, methylphenidate IR, dexmethylphenidate XR, and methylphenidate XR, regardless of the galenic formulation
(2) Amphetamine derivative: Amphetamine, lisdexamfetamine, and dextroamphetamine, regardless of the galenic formulation
(3) Atomoxetine
(4) Clonidine
(5) Guanfacine
(6) Bupropion
(7) Modafinil
(8) Viloxazine

The treatment nodes will be as follows:

Dosing schedule

Fixed-dose trials are characterized by the assignment of participants to pre-specified doses without considering their individual response or tolerability. In such trials, the targeted maximum dose may be reached at a slower pace if tolerability symptoms arise. The treatment strategy for fixed-dose trials involves "targeting dose j for treatment k, regardless of efficacy and tolerability." For our primary analysis, only fixed dosing schedules will be employed.

On the other hand, flexible-dose trials involve the random assignment of participants to groups with doses determined individually based on efficacy or tolerability. To draw a causal interpretation of individual doses, time-dependent confounding factors and individual participant data are necessary. However, we will carefully incorporate flexible doses as sensitivity analyses. To be included in our analysis, a flexible-dose study must clearly specify the maximum intended dose at baseline. Thus, for both fixed and flexible dosing strategies, the intention is to reach the maximum targeted dose at the time of randomization. We acknowledge that this strategy involves heterogeneity in the steps taken to achieve the maximum targeted dose, such as adapting doses based on safety or efficacy.

We may exclude certain treatment nodes from the primary analysis due to a scarcity of data, specifically when only employing a fixed dosing schedule.

Conversion doses

We will use the same conversion doses from Farhat et al. [16] (see Appendix Table S3). When doses in mg/kg/day will be reported, we will convert to mg/day using the mean baseline weight of the study participants.

Dose–effect network *meta*-analysis model

We will define the DE-NMA model as a three-level hierarchical model [17]. Assume each study i with treatment k at dose j reports the mean of a continuous outcome, y_{ijk}, and standard error se_{ijk}. The sample means, y_{ijk}, are assigned a normal distribution with likelihood as follows:

$$y_{ijk} \sim N(\varphi_{ijk}, \sigma^2_{ijk})$$

where

$\varphi_{ijk} = \theta_{ijk} \times s_i$;

θ_{ijk} is the standardized mean (SM) and s_i is the pooled standard deviation. Then, we parametrize as follows:

$$\theta_{ijk} = \mu_i + \delta_{ijk}$$

where μ_i is the study-specific mean outcome in the placebo (or reference) arm in study i and δ_{ijk} is the study-specific treatment effect (standardized mean difference) of treatment k at dose level j versus placebo. If the study i does not have a placebo arm, we will choose a reference treatment R at the minimum dose level r as the study-specific reference.

The parameter δ_{ijk} will be modelled assuming exchangeable effects:

$$\delta_{ijk} \sim N\left(\Delta_{ijk}, \tau^2\right)$$

With τ^2 representing between-studies variability, assumed equal across all treatment comparisons.

The dose–effect shape will be modelled using a restricted cubic spline (denoted with F) with three knots, placed at 25%, 50%, and 75% of the observed dose range per drug:

$$\Delta_{ijk} = F(x_{ijk}; \beta_{1k}, \beta_{2k}).$$

Sensitivity analyses

The following sensitivity analyses will be performed:

1. Excluding studies where all participants have IQ < 70
2. Excluding studies lasting < 2 weeks
3. Excluding crossover trials
4. Including only low risk of bias study according to RoB
5. Splitting amphetamine and lisdexamfetamine
6. Modify the number and the position knots of the restricted cubic splines
7. Modify prior distributions

Discussion

With this dose–response network meta-analysis, we aim to better understand the dose–response relationship of pharmacological treatment in ADHD which could help clinician to the identification of optimal doses. This endeavor is pivotal for advancing personalized treatment strategies, ensuring both enhanced therapeutic outcomes and reduced side effects for individuals with ADHD.

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
DE-NMA	Dose-effect network meta-analysis
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDA	Food and Drug Administration
HKD	Hyperkinetic disorder
IR	Immediate release
NMA	Network meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
RCT	Randomized controlled trials
RoB	Risk of bias
XR	Extended release

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02675-1.

Additional file 1. Appendix: Table S1 PRISMA-P checklist. Additional details on search strategy: Search in electronic sources. Table S2: washout periods. Table S3 : conversion factors for stimulants [1].

Acknowledgements

Not applicable.

Authors' contributions

MN and LJ wrote the first draft of this manuscript. All authors revised the manuscript. All authors participated in the study design.

Funding

The submission fees are covered by the Hospices Civil de Lyon (HCL). Samuele Cortese, NIHR Research Professor (NIHR303122), is funded by the NIHR for this research project. Samuele Cortese is also supported by NIHR grants NIHR203684, NIHR203035, NIHR130077, NIHR128472, and RP-PG-0618-20003 and by grant 101095568-HORIZONHLTH-2022-DISEASE-07-03 from the European Research Executive Agency. Andrea Cipriani 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, by the NIHR Oxford Health Biomedical Research Centre (grant NIHR203316), and by the Wellcome Trust (GALENOS project). 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 and Social Care.

Availability of data and materials

Data and code will be available at OSF repository.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
M. N., L. J., G. S., A. C., F. S., O. E., and T. H. declare that they have no competing interests. S. C. has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, and from Healthcare Convention for educational activity on ADHD and has received honoraria from Medice

Received: 29 April 2024 Accepted: 30 September 2024
Published online: 12 October 2024

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