**Comparative efficacy and tolerability of medications for**

**Attention-Deficit/Hyperactivity Disorder in children, adolescents and adults:**

**a systematic review and network meta-analysis**

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**RESEARCH IN CONTEXT**

**Evidence before this study**

Over the past few decades, there has been a substantial increase in the prescription rates of medications for ADHD across many countries. However, the benefits and safety of these medications remain matter of considerable debate in the scientific literature. Furthermore, published meta-analyses of head-to-head trials as well as network meta-analyses provide inconsistent findings on the comparative benefits and harms of ADHD medications.

**Added value of this study**

This study, based on the most advanced methodology for network meta-analyses, represents the most comprehensive synthesis to date on the comparative efficacy and tolerability of medications for ADHD across age groups. Differently from previous network meta-analyses of ADHD treatments, we have in addition to published data, also included unpublished data which was systematically gathered from study authors, regulatory agencies’ websites, and drug manufacturers, using a common set of inclusion criteria for trials in children, adolescents, and adults. We focused on a series of clinically relevant outcomes, namely, efficacy on ADHD core symptoms, global clinical functioning, tolerability, effects on weight and blood pressure, and acceptability. We also explored the impact of a number of important effect modifiers, such as dose and comorbidities. We found that all included medications (with the exception of modafinil in adults) were more efficacious than placebo for the acute treatment of ADHD. Medications for ADHD tended to be less efficacious and less well tolerated in adults than in children/adolescents. However, included drugs were not equivalent and their profile in terms of efficacy, tolerability and acceptability varied across age groups. Taking into account all study outcomes, evidence from this network meta-analysis supports methylphenidate, in children and adolescents, and amphetamines, in adults, as the preferred first pharmacological choice for the short-term pharmacological treatment of ADHD. We retained only a limited number of studies with outcomes beyond 12 weeks.

**Implications of all the available evidence**

This network meta-analysis should inform future guidelines and daily clinical decision making on the choice of medications for ADHD across the age range, along with available evidence on cost-effectiveness and considering patients’ preferences. The paucity of trials with randomized outcomes beyond 12 weeks highlights the need to fund further studies to assess long-term effects of these drugs. Furthermore, future research should include individual-patient data in network meta-analyses of ADHD medications, which will allow a more reliable estimation of predictors of individual response, thus contributing to the science of precision medicine in ADHD.

**ABSTRACT**

**BACKGROUND**

The benefits and safety of ADHD medications for Attention-Deficit/Hyperactivity Disorder (ADHD) remain controversial and guidelines are inconsistent on which medications are to be preferred across different age groups. We aimed to estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.

**METHODS**

We searched PubMed, BIOSIS Previews, CINAHL, Cochrane Library, EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science, international trial registries, drug manufacturers’ and regulatory agencies’ websites until April 7th, 2017 for published and unpublished double-blind randomised controlled trials (RCTs) comparing amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo. Study authors and drug manufacturers were systematically contacted for additional information. Primary outcomes were efficacy (change in severity of ADHD core symptoms based on teachers’ and clinicians’ ratings) and tolerability (proportion of patients who dropped out due to side effects) at time points closest to 12, 26 and 52 weeks.

We estimated summary odds ratios (ORs) and standardized mean differences (SMDs) using pairwise- and network- meta-analysis with random effects. The risk of bias of individual studies was assessed using the Cochrane Risk of Bias tool and the confidence of estimates (certainty of evidence) was assessed using GRADE. This study is registered with PROSPERO (CRD42014008976).

**FINDINGS**

Overall, 133 double-blind RCTs (81 in children/adolescents, 51 in adults, and one in both) were included. Analysis of efficacy closest to 12 weeks was based on 10,068 children/adolescents and 8,131 adults, and, for tolerability, on 11,018 and 5,362 participants, respectively. The confidence of estimates varied from high or moderate (for some comparisons) to low or very low (for the majority of the indirect comparisons). For ADHD core symptoms rated by clinicians in children/adolescents closest to 12 weeks, all included drugs were superior to placebo [SMD ranging between -1.02, (95% CI -1.19 to -0.85) for amphetamines and -0.56 (-0.66 to -0.45) for atomoxetine; methylphenidate: -0.78, -0.93 to -0.62)]; in contrast, for comparisons based on teachers’ ratings, only methylphenidate (-0.82, -1.16 to -0.48) and modafinil (-0.76, -1.15 to -0.37) were more efficacious than placebo (no data were available for the amphetamines and clonidine). In adults (clinicians’ ratings), amphetamines (-0.79, -0.99 to -0.58), methylphenidate (-0.49, -0.64 to -0.35), bupropion (-0.46, -0.85 to -0.07) and atomoxetine (-0.45, -0.58 to -0.32), but not modafinil (0.16, -0.28 to 0.59), were better than placebo. As for tolerability, amphetamines were inferior to placebo in both children/adolescents (OR 2.30, 95% CI 1.36 to 3.89) and adults (3.26, 1.54 to 6.92), guanfacine was inferior to placebo in children/adolescents (2.64, 1.20 to 5.81), whereas atomoxetine (2.33, 1.28 to 4.25), methylphenidate (2.39, 1.40 to 4.08) and modafinil (4.01, 1.42 to 11.33) were less well tolerated than placebo only in adults. In head-to-head comparisons, only differences in efficacy (clinicians’ ratings) were found, favouring amphetamines over modafinil, atomoxetine and methylphenidate in both children/adolescents (SMDs ranging between -0.46 and -0.24) and adults (between -0.94 and -0.29). We did not find sufficient data for the longer 26 and 52-week time points.

**INTERPRETATION**

Our findings represent the most comprehensive available evidence-base to inform patients, families, clinicians, guideline developers and policy-makers on the choice of ADHD medications across age groups. Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate, in children/adolescents, and amphetamines, in adults, as preferred first choice medications for the short-term treatment of ADHD. New research should urgently be funded to assess long-term effects of these drugs.

**FUNDING**

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**Keywords:** ADHD; pharmacological treatment; stimulants; network meta-analysis

**INTRODUCTION**

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by age-inappropriate and impairing levels of inattention and/or hyperactivity/impulsivity.1 It is estimated to affect around 5% of school-age children2 and 2.5% of adults worldwide.3 Annual incremental costs of ADHD have been estimated at $143-$266 billion in the US4 and are substantial in other countries as well.5, 6 Available pharmacological treatments for ADHD include psychostimulant (i.e., methylphenidate and amphetamines) and non-psychostimulant medications. In the past few decades, prescription rates of ADHD drugs have increased significantly both in the US7 and other countries.8 However, even though recommended in clinical guidelines,9-14 the efficacy and safety of ADHD medications remain controversial.15-17 Furthermore, current guidelines are inconsistent in their treatment recommendations.9-14 Whilst some rank methylphenidate over amphetamines(e.g.9, in children), others recommend *psychostimulants* as first line treatment without any distinction being made.10,11 Additionally, the non-psychostimulant atomoxetine is variously recommended as third9, second10,11 or potentially first-line treatment12 across the various available guidelines. The methods used for sequencing these recommendations are not always specified and most commonly, including the recent 2018 NICE Guidelines,9 incorporate national drug licencing regulatory approval and cost-effectiveness with expert opinion in conjunction with the few head-to-head comparisons that are available.

Network meta-analyses (NMAs) facilitate estimation of the comparative efficacy and tolerability of two or more interventions even when they have not directly been investigated head-to-head in randomised controlled trials (RCTs).18 As a consequence, compared to standard, pairwise meta-analyses, NMAs have been found to increase the precision of the estimates.18 Previous NMAs in ADHD have focused on either children/adolescents19-24 or on adults only25-28, have often chosen to compare only a limited number of drugs24, 25, 27, 29 or have addressed exclusively the safety of treatments.26

To fill this gap, we conducted a systematic review and NMA of double-blind RCTs in children/adolescents and adults with ADHD, using data from published reports as well as unpublished data systematically gathered by drug manufacturers or study authors. We specifically aimed to compare ADHD medications in terms of efficacy on core ADHD symptoms, clinical global functioning, tolerability, acceptability, and other clinically important outcomes, i.e., blood pressure and weight changes.

**METHODS**

The protocol was registered with PROSPERO (CRD42014008976) and published.30 We followed the PRISMA extension for NMAs.31

***Data Sources and Searches***

We searched PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials, EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations & Theses: UK & Ireland, ProQuest Dissertations & Theses A&I, and the WHO International Trials Registry Platform, including ClinicalTrials.gov, from the date of their inception to April 7, 2017, with no language restrictions. We used 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 ADHD medications (see Appendix 1 for full details). The Food and Drug Administration,32 European Medicines Agency,33 and relevant drug manufacturers’ websites, as well as reference of previous systematic reviews/guidelines, were hand-searched for additional information. We also contacted study authors and drug manufacturers to gather additional unpublished information/data (see Appendix 1).

***Study Selection***

Double-blinded RCTs (parallel-group, cross-over, or cluster), lasting at least 1 week, including children (≥5 and <12 years), adolescents (≥12 and <18 years) or adults (≥18 years) with a primary diagnosis of ADHD according to DSM-III, DSM III-R, DSM-IV(TR), DSM-5, ICD-9 or 10, were eligible. There were no restrictions on ADHD subtype/presentation, gender, IQ, socio-economic status, or comorbidities (except for comorbidities requiring concomitant pharmacotherapy). Studies were included if they assessed any of the following medication, as oral monotherapy, compared to each other or with placebo: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate (including dexmethylphenidate), or modafinil. Studies with enrichment designs (e.g., trials selecting drug responders only following a ‘run-in’ phase) were excluded, as they can potentially inflate efficacy and tolerability estimates. See Appendix 2 for full inclusion/exclusion criteria.

For our primary analyses, we considered:

1. *efficacy*, measured as the change in severity of ADHD core symptoms based on clinicians’ ratings for children, adolescents and adults. See Appendix Table 1 for a list of rating scales considered for inclusion. For children/adolescents, teachers’ ratings were also considered as a primary efficacy outcome because they provide a complementary view to clinicians’ ratings and information from multiple raters, increases the validity of ADHD diagnosis;34
2. *tolerability*, i.e., the proportion of participants who left the study due to any side effects.

Secondary outcomes included: change in severity of ADHD core symptoms based on parents’ ratings for children/adolescents and self-reports for adults; clinical global functioning, measured by the Clinical Global Impression-Improvement (CGI-I, clinicians’ ratings); acceptability, i.e., the proportion of participants who left the study for any reason; and change in weight and blood pressure. Outcomes were those available at the time closest to 12 (primary endpoint), 26 and 52 weeks.

***Data Extraction and Quality Assessment***

Data were extracted by at least two independent investigators. Risk of bias was assessed using the Cochrane risk of bias tool.35 The certainty of evidence was estimated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)approach for NMAs (Appendix 3).36

***Data Synthesis and Analysis***

All analyses were conducted separately for studies in children/adolescents and adults, respectively. First, pairwise meta-analyses (active drug vs placebo, or active drug vs another active drug) were conducted for all outcomes and comparisons at each available time point, using a random-effects model.37 Standardized mean difference (SMD) Hedges’s adjusted *g* and odds ratio (OR), with relative 95% confidence intervals, were calculated for continuous and dichotomous outcomes, respectively. Statistical heterogeneity within each pairwise comparison was assessed by calculating the I-squared statistic and its confidence intervals.38 Second, network meta-analyses were performed within a frequentist framework assuming equal heterogeneity parameter τ across all comparisons and accounting for correlations induced by multi-arm studies.39, 40 The assessment of statistical heterogeneity in the entire network was based on the magnitude of the common τ2 estimated from the NMA models.41 The magnitude of the heterogeneity variance was compared with the empirical distribution.42, 43 The loop-specific approach44 and the ‘design-by-treatment’ model45 were used to evaluate incoherence locally and globally, respectively. A hierarchy of the competing interventions was established using the Surface Under the Cumulative RAnking curve (SUCRA) and Mean ranks.46 A set of subgroup/sensitivity analyses were planned to assess the impact of clinical/study design effect modifiers, such as duration of the study, gender, age (children *vs.* adolescents), psychiatric comorbidities, intelligence quotient (IQ), cross-over design, medication status, industry sponsorship, inequalities in doses, risk of bias, and data imputation (see protocol30). The primary analysis was limited to studies using medications within the therapeutic range (as per the FDA recommendations, where applicable). Additionally, we explored effects at different dose regimens in two sets of *sensitivity* analyses: 1) excluding the studies that did not use the FDA-licensed dose (see Appendix Tables S3 and S4); 2) including also the studies that used dose ranges recommended in national or international guidelines/formularies and that differed from the FDA recommendations. Finally, to explore possible differences between lisdexamfetamine and the other amphetamines, we conducted a *post-hoc* analysis separating the two compounds, since lisdexamfetamine is metabolized differently from other amphetamines, which may impact its efficacy and tolerability.47 All analyses were performed using STATA v.14. Additional details are reported in Appendices 4-5 and Appendix Tables 3-7. Appendix 6 lists the changes to the original protocol. The study was done from January 11th 2014 to September 9th 2017, and data analysis were conducted from September 10th 2017 to February 24th 2018.

**Data sharing**

With the publication of this article, the full dataset will be freely available online in Mendeley Data, a secure online repository for research data, which allows archiving of any file type and assigns a permanent and unique digital object identifier (DOI) so that the files can be easily

Referenced (DOI to be added).

**Role of the funding sources**

The funder of this study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. SCo, NA, CDG and AC had full access to all the data, and AC was responsible for the decision to submit for publication.

**RESULTS**

The study selection process is shown in Figure 1, and reported in detail in Appendix 7 (list of excluded studies, with reasons for exclusion) and Appendix 8 (list of retained studies). Studies retained for the NMA (n= 133, 81 in children/adolescents, 51 in adults, and one including both children/adolescents and adults) included a total of 14,346 children/adolescents and 10,296 adults (see PRISMA flowchart). For 83% of the studies, we used additional data/information not reported in the full-text paper. Appendix tables 8-10 report the main characteristics of the included studies. As shown in Appendix Table 11, 23.5%, 65.4%, and 11.1% of studies in children/adolescents and 27.5%, 56.8% and 15.7% in adults were rated at overall *low*, *unclear*, and *high* risk of bias, respectively.

Figure 2 shows the network plots for the primary outcomes closest to 12 weeks. Network plots for secondary outcomes are reported in Appendix figure 1. Results of the pairwise meta-analyses, and related heterogeneity, are reported in Appendix table 12. Results of the NMAs on the primary outcomes at 12 weeks are shown in Figures 2-4 and Appendix table 13. Figure 3 also reports the confidence of estimates for each comparison. Figure 4 summarizes data on efficacy (10,068 and 8,131 participants in children/adolescent and adults, respectively) and tolerability (11,018 and 5,362 participants in children/adolescent and adults, respectively).

For ADHD core symptoms rated by clinicians in children/adolescents, all drugs were superior to placebo (amphetamines: SMD -1.02, 95% CI -1.19 to -0.85, bupropion: -0.96, -1.69 to -0.22, methylphenidate: -0.78, -0.93 to -0.62, clonidine: -0.71, -1.17 to -0.24, guanfacine: -0.67, -0.85 to -0.50, modafinil: -0.62, -0.84 to -0.41, and atomoxetine: -0.56, -0.66 to -0.45). In adults, amphetamines (-0.79, -0.99 to -0.58), methylphenidate (-0.49, -0.64 to -0.35), bupropion (-0.46, -0.85 to -0.07), and atomoxetine (-0.45, -0.58 to -0.32), but not modafinil (0.16, -0.28 to 0.59), were superior to placebo (no data were available for guanfacine and clonidine). In both children/adolescents and adults, amphetamines were significantly superior to modafinil (children: -0.39, -0.67 to -0.12; adults: -0.94, -1.43 to -0.46), atomoxetine (children: -0.46, -0.65 to -0.27; adults: -0.34, -0.58 to -0.10), and, marginally, methylphenidate (children: -0.24, -0.44 to -0.05; adults: -0.29, -0.54 to -0.05). Additionally, in children/adolescents, amphetamines were superior to guanfacine (-0.35, -0.59 to -0.10) and methylphenidate was, marginally, superior to atomoxetine (-0.22, -0.39 to -0.05). In adults, methylphenidate (-0.65, -1.11 to -0.19), atomoxetine (-0.61, -1.06 to -0.15) and bupropion (-0.62, -1.20 to -0.03) were superior to modafinil. In contrast, according to teachers’ ratings of children, only methylphenidate (-0.82, -1.16 to -0.48) and modafinil (-0.76, -1.15 to -0.37) were superior to placebo (no data were available for the amphetamines and clonidine; atomoxetine: -0.32, -0.82 to 0.18).

In children/adolescents, only guanfacine (OR 2.64, 95% CI 1.20 to 5.81) and amphetamines (2.30, 1.36 to 3.89) were less well tolerated than placebo. In adults, modafinil (4.01, 1.42 to 11.33), amphetamines (3.26, 1.54 to 6.92), methylphenidate (2.39, 1.40 to 4.08), and atomoxetine (2.33, 1.28 to 4.25) were inferior to placebo (no data were available for guanfacine and clonidine). No significant differences were found among active drugs, in children/adolescents and adults.

In children/adolescents, the common heterogeneity SD for efficacy (teachers’ and clinicians’ ratings), and tolerability was 0.355, 0.188, and 0.268, respectively. In adults, the common heterogeneity SD for efficacy rated by clinicians and tolerability was 0.178 and 0.282, respectively. The test of global inconsistency did not show any significant difference for the primary outcomes. Additional details are reported in Appendix table 14.

For parents’ ratings of children and adults’ self-ratings of ADHD core symptoms, efficacy of active drugs versus placebo was similar to those for the clinicians’ ratings, except that guanfacine, according to parents’ ratings (SMD -0.23, -0.90 to 0.45) and bupropion, for both parents’ (0.24, -0.44 to 0.92) and self-reports (-0.30, -0.61 to 0.01), were not superior to placebo (Appendix Table 15).

In children/adolescents, all compounds, except clonidine (OR 2.78, 0.91 to 8.53), were superior to placebo. In adults, only amphetamines (4.86, 3.30 to 7.17), bupropion (3.43, 1.45 to 8.14), and methylphenidate (3.08, 2.04 to 4.65) were superior to placebo.

Amphetamines (children/adolescents: -0.71, -1.15 to -0.27; adults: -0.60, -1.03 to -0.18), methylphenidate (children/adolescents: -0.77, -1.09 to -0.45; adults: -0.74, -1.20 to -0.28) and, additionally, atomoxetine (SMD -0.84, -1.16 to -0.52) and modafinil (-0.93, -1.59 to -0.26) in children/adolescents, significantly decreased weight compared to placebo.

Amphetamines (SMD 0.09, 0.01 to 0.18) and atomoxetine (0.12, 0.02 to 0.22) in children/adolescents and methylphenidate (0.17, 0.05 to 0.30), in adults, significantly increased blood pressure compared to placebo. For diastolic pressure, amphetamines (0.21, 0.12 to 0.31), atomoxetine (0.28, 0.18 to 0.37), and methylphenidate (0.24, 0.14 to 0.33) in children/adults and atomoxetine (0.19, 0.08 to 0.30) and methylphenidate (0.20, 0.08 to 0.32), in adults, significantly increased blood pressure compared to placebo.

Methylphenidate (OR 0.69, 0.52 to 0.91), in children/adolescents, and amphetamines, in adults (0.68, 0.49 to 0.95), were significantly better than placebo.

For those variables for which sufficient data were available (impact of study length, comorbidities, IQ, cross-over design, unfair dose comparisons, and data imputation), findings were generally robust to the subgroup/sensitivity analyses (Appendix table 16). Due to paucity of data, we could not properly assess the impact of gender, age (children *vs.* adolescents), low risk of bias, medication status, and industry sponsorship. Sensitivity analyses exploring the impact of different maximum doses confirmed the results of the primary dose analysis (Appendix table 17).

*Post hoc* analyses separating lisdexamfetamine from the other amphetamines highlighted some differences. In particular, in children, lisdexamfetamine (OR 2.69, 95% CI 1.40 to 5.16), but not the other amphetamines (1.83, 0.84 to 4.02), was less well tolerated than placebo, whereas in adults, the opposite pattern emerged (lisdexamfetamine: 2.74, 0.80 to 9.30; other amphetamines: 3.66, 1.36 to 9.87). NMA heterogeneity for the *dose* and *post hoc* analyses is reported in Appendix table 18.

Details on NMA inconsistency and SUCRA/Mean rank are reported in Appendix table 19 and 20, respectively. Empirical heterogeneity variance for continuous outcomes for drugs vs placebo comparisons was 0.05 (50% percentile) and 0.24 (75% percentile); for binary outcomes it was 0.12 (50% percentile) and 0.34 (75% percentile). Funnel plots are shown in Appendix Figure 2. We retained only a limited number of studies, all in adults, with reported outcomes closest to 26 or 52 weeks (Appendix table 21); therefore results for these outcomes were deemed not informative.

As detailed in Appendix table 22 and in Appendix figures 3-5, the confidence in estimate for the primary outcome comparisons was rated as *very low, low, moderate, and high,* respectively, in 13, 18, 10, and 1out of 42 mixed comparisons (i.e., combining direct and indirect evidence) and *very low*, *low*, and *moderate*, respectively, in 37, 20, and 2 out of 59 indirect comparisons.

**DISCUSSION**

This NMA represents the most comprehensive comparative synthesis to date on the efficacy and tolerability of medications for children/adolescents and adults with ADHD. It addresses the limitations of previous NMAs which focused selectively on children/adolescents19-24 or adults25-28, included only published material21-24, 26, non-blinded trials19, 21-24, or non-core ADHD outcomes.19, 22, 25, 28

Overall, all medications, except modafinil in adults, were more efficacious than placebo for the short-term treatment of ADHD, and less efficacious as well as less well tolerated in adults than in children/adolescents. However, included medications were not equivalent in relation to their mean effect size, which ranged from moderate to high and varied according to the type of rater. Furthermore, even though amphetamines were the most efficacious compounds both in children/adolescents and adults, the effects of medications varied across different age groups in a number of outcomes. As for tolerability, in children, only amphetamines and guanfacine were less well tolerated than placebo, whilst in adults methylphenidate, amphetamines, and atomoxetine were worse than placebo. Additionally, amphetamines significantly increased diastolic blood pressure in children/adolescents, but not in adults. In children/adolescents, methylphenidate was the only drug with better acceptability than placebo; in adults this was the case only for amphetamines. Atomoxetine had the lowest mean effect size in children/adolescents based on clinician ratings, but in adults its efficacy on ADHD core symptoms was comparable to that of methylphenidate. The large confidence interval in relation to the efficacy and tolerability of bupropion, clonidine, guanfacine and modafinil suggests that caution should be used when interpreting these data. Another relevant finding, that requires replication in head-to-head trials, is the lack of significant differences between amphetamines and methylphenidate on the clinical global impression (CGI) measure.

Taking into account all the included outcomes, our results support methylphenidate in children/adolescents, and amphetamines, in adults, as the first pharmacological choice for ADHD. In fact, in adults, amphetamines were: 1) the most efficacious compounds as rated by clinicians and by self-report; 2) as well tolerated as methylphenidate, and 3) the only compounds with better acceptability than placebo. In children/adolescents, even though amphetamines were marginally superior to methylphenidate according to clinicians’ rating, methylphenidate was the only compound with better acceptability than placebo and, unlike amphetamines, was not worse than placebo in terms of tolerability. Additionally, our results on secondary outcomes highlight the importance of monitoring weight and blood pressure changes with atomoxetine as much as with stimulants.

Our conclusions from this analysis concur only in part with the recent NICE guidelines9. NICE recommends methylphenidate as the first choice in children/adolescents and methylphenidate *or* lisdexamphetamines as first choice in adults. Additionally, whilst NICE recommend atomoxetine *or* guanfacine as possible third line choice in children, our results suggest that, despite comparable efficacy on ADHD core symptoms rated by parents, atomoxetine was equal to placebo in terms of tolerability, whilst guanfacine was worse. However, it should be noted that the NICE recommendations were informed not only by empirical evidence, but also by considerations on costs and licence, as well as flexibility of formulations.

Whilst the *post hoc* analyses did indicate differences between the amphetamine prodrug lisdexamfetamine and the other amphetamines, the limited number of studies that we were able to include in this comparison (children/adolescents: lisdexamfetamine: n=4; amphetamines: n=1; adults: lisdexamfetamine: n=2; amphetamines: n=1) prevent us from drawing any firm conclusions from these findings. We would therefore not feel confident at this stage to recommend lisdexamfetamine over the other amphetamines for adults, as was suggested by NICE, although on the basis of UK costs.9

An important factor to consider in the interpretation of our findings is the medication dose. Indeed, there is considerable inter-individual variation in terms of most effective dose. In general, we found no substantial differences in either efficacy or tolerability across the various medications when the maximum allowed dose was that defined by the FDA or by guidelines (suggesting in general higher maximum doses than FDA). We excluded some studies9, 48, 49 because they included doses higher than those recommended in available guidelines, thus poorly reflecting common clinical practice. It is possible that the inclusion of these studies would have changed the efficacy and the tolerability results.

In general, results for the primary outcomes were robust to our sensitivity analyses, suggesting that short duration trials (< 3 weeks), presence of psychiatric comorbidities or low IQ as inclusion criterion, dose comparisons that we considered unfair, cross-over design, and missing data imputation did not significantly impact the results.

Our study has some limitations. Whilst we did our best to include all available trials and retrieve unpublished data, we cannot rule out the possibility of missing information. A limitation is that the latest update of studies included in the NMA was in April 2017. We conducted a PubMed search in May 2018 and found only three addition al studies that met our inclusion critieria.50-52 Given that we already had 133 included studies, we decided that adding these three studies would not have materially changed the final results. Additionally, some nodes in our network included only a small number of studies. Indeed, to adhere to the assumption of transitivity and reduce the risk of biased estimates (for instance, those that included enrichment designs), we had to discard a large number of studies that were initially selected as potentially relevant (Appendix 7). The majority of included studies compared an active drug to placebo and the number of actual head-to-head trials was quite small, so comparative efficacy between interventions was often based on indirect comparisons.

We found significant statistical heterogeneity in the pairwise meta-analyses and the study population in our review included subjects with different rates of previous exposure and response to ADHD medications. These characteristics were quite evenly distributed across the included studies and across the different nodes in the network, so, even if they contributed to the statistical heterogeneity, it is unlikely that they have implications in terms of clinical heterogeneity and impacted on the validity of our results. On the contrary, this can be seen as increasing the external validity of our findings, as the patients seen in real-world clinical practice tend to have similar variations. Although we included studies that used different rating scales to assess the core symptoms of ADHD, we carefully selected only validated scales that measure exclusively the same triad of symptoms, i.e., inattention, hyperactivity, and impulsivity.

Our results should also be considered in light of the risk of bias of individual studies and GRADE quality ratings. Importantly, after gathering additional unpublished information, the overall number of unclear items across all items of the Risk of Bias decreased from 63.5% to 35.2%. This points to an urgent need for a more complete and open reporting in the field. Additionally, the confidence of estimate for primary outcomes was low/very low in a number of comparisons, reducing the certainty of the findings. The majority of *very low* ratings were for indirect comparisons, suggesting the need for additional well designed head-to-head studies. Whereas previous pairwise (e.g.16, 53) or network meta-analyses (e.g.19) of ADHD medications rated *all* comparisons at *low/very low* quality, due in part to additional unpublished information that we gathered and a more nuanced assessment, we could rate *some* comparisons at *high* or *moderate* quality. Of note, these included the most commonly used drugs for ADHD (i.e., methylphenidate and amphetamines). Additionally, our stringent criteria for the risk of bias (a study was assessed at overall *low* risk only when all individual items were at *low* risk) may have contributed to downgrade the final GRADE ratings.

We planned to conduct analyses for outcomes closest to 12, 24 and 52 weeks, but few data were available and this analyses were therefore not possible. The lack of data reflects the ethical issues associated with conducting long-term placebo controlled RCTs of effective treatments. Thus, our findings can only inform the choice of short-term medication treatment for ADHD. Additionally, due to a paucity of data, we were unable to properly conduct all of the planned sensitivity analyses. Finally, we did not include studies of antipsychotic or tricyclic antidepressant compounds because, whilst commonly prescribed for those with ADHD, they are not routinely used to treat ADHD core symptoms and their inclusion would therefore violate the assumption of transitivity in the networks.

Notwithstanding these caveats, our findings represent the best currently available evidence-base (not constrained by local costs and licencing) to inform future guidelines internationally and shared decision-making between patients, carers, and clinicians, where a balance has to be made between efficacy and tolerability of ADHD medications.

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Drs Cortese and Cipriani had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**DECLARATION OF INTEREST**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf (available on request from the corresponding authors) and declare: Dr Cortese reports receiving reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non-profit organization, in relation to lectures that he delivered for ACAMH and by Healthcare convention for educational activity on ADHD. Dr Adamo reports receiving travel support to attend a conference by Shire. Dr Mohr-Jensen reports receiving fees as a speaker for HB and Pharma/Medice. Dr Carucci reports travel supports from Shire and collaborating as sub investigator in a clinical trial funded by Shire. Dr Banaschewski reports serving in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, Otsuka, PCM scientific, Shire and Viforpharma, receiving conference support or speaker’s fee by Medice, Novartis and Shire and being involved in clinical trials conducted by Shire & Viforpharma and receiving royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. Dr Coghill reports receiving grants and personal fees from Shire and Servier, personal fees from Eli Lilly, grants from Vifor, personal fees from Novartis, and personal fees from Oxford University Press. Dr Hollis and Simonoff report being members of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group. Dr Zuddas reports receiving honoraria for participating to Advisory board or Data Safety Monitory Boards from Eli Lilly, Otsuka, Lundbeck, Takeda and EduPharma, receiving royalties from Oxford University Press and Giunti OS, and receiving research grants from Lundbeck, Roche, Shire and Vifor. Dr Steinhausen reports working as an advisor and speaker for the following pharmaceutical companies: Janssen-Cilag, Eli Lilly, Novartis, Medice, Shire and UCB and receiving unrestricted grants for postgraduate training courses or conferences and research by Janssen-Cilag, Eli Lilly, Novartis, Medice and Swedish Orphan International, as well as book royalties from Cambridge University Press, Elsevier, Hogrefe, Huber, Klett and Kohlhammer Publishers. Dr Cipriani is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility. No other disclosures were reported.

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**FIGURE CAPTIONS**

**Table 1: Effect of ADHD drugs in children and adults at time points closest to 12 weeks in terms of efficacy as rated by clinicians (in dark blue) or teachers (in light blue), and in terms of tolerability (in gray).** *Legend: Drugs are reported in alphabetical order. Results are based on network estimates (there are no data about clonidine and guanfacine in the upper triangle, because there are no studies testing these two drugs in adults). The SMDs (with 95% CI) in the column-defining treatment compared with the row-defining treatment. Negative SMDs (lower than zero) favor the column-defining treatment in children/adolescents and the row-defining treatment in adults. Significant results are underscored. OR=Odds Ratio. SMD=Standardized Mean Difference. CI=Confidence Interval. \*Moderate quality of evidence. †Low quality of evidence. ‡Very low quality of evidence. § High quality of evidence*

**Figure 1: Network of eligible comparisons for efficacy and tolerability in children, adolescents and adults.**

*Legend: The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). The number of trials for pairs of treatments ranged from 22 (methylphenidate vs. placebo, tolerability, children/adolescents) to one (several comparisons)*

**Figure 2: Forest plots of network meta-analysis results including all trials for efficacy and tolerability compared to placebo as reference compound.**

*Legend: OR: Odds Ratio; SMD: Standardized Mean Difference; CI: Confidence Interval. (In red statistically significant results favouring active drugs, in light blue statistically significant results favouring placebo)*

**Figure 4: Two-dimensional graphs about efficacy and tolerability in studies in children/adolescents (top) and adults (bottom).**

*Legend: Effects for individual drugs are represented by coloured nodes, with corresponding confidence interval (bars).*