Pharmacological interventions for ADHD: a systematic review and dose–effect network meta-analysis

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Summary

Background Optimising the dosage of pharmacological treatments for ADHD is key to maximising their benefits, yet most clinical guidelines provide only limited information on this issue. Dose–effect relationships have not been comprehensively assessed across all ADHD medications and age groups, despite growing concerns about subtherapeutic prescribing. We aimed to estimate dose–effect curves for efficacy and tolerability of ADHD medications (stimulants and non-stimulants) across age groups.

Methods We conducted a systematic review and dose–effect network meta-analysis of double-blind randomised controlled trials (RCTs) evaluating oral monotherapy (stimulants and non-stimulants) in individuals aged 5 years and older meeting standardised ADHD criteria. Studies involving genetic syndromes, treatment-resistant populations, or withdrawal-phase designs were excluded. We retrieved eligible studies from the MED-ADHD database, updated on Feb 17, 2025, without language restrictions. We included published and unpublished aggregated-level data. The primary outcome was efficacy (measured using validated clinical scales) and the secondary outcome was tolerability (discontinuation due to adverse events). Within-study bias was assessed with the Cochrane Risk of Bias Tool (version 2). We summarised dose–effect associations using a hierarchical Bayesian model with restricted cubic splines. Separate analyses were conducted for children or adolescents (aged <18 years) and adults (aged ≥18 years). The distribution of key effect modifiers was used to examine transitivity of the network. People with lived experience were involved in the conceptualisation and design of the study, and in the interpretation of the findings. The protocol was pre-registered on OSF.

Findings Our 2017 search identified 9948 potential references for inclusion and our Feb 17, 2025 search identified 5148 references. Of these 15 096 references, 8467 were excluded after title and abstract screening, and a further 5862 references were excluded after a full-text read. Of the 767 remaining reports, 164 were included in the systematic review and 113 RCTs (45 in adults and 68 in children and adolescents) were included in the dose–effect network meta-analysis. The 68 RCTs on children and adolescents included 14 138 participants (9981 [70·6%] males and 4157 [29·4%] females) and the 45 RCTs on adults included 11 016 participants (5958 [54·0%] males and 5056 [46·0%] females). Data on ethnicity or race were inconsistently reported across RCTs. We found distinct dose–effect patterns by medication class and age group. In children and adolescents, methylphenidate, amphetamines, and guanfacine showed increasing median efficacy up to 45 mg/day, 25 mg/day and 4 mg/day, respectively, with no evidence of additional benefit at higher doses, although estimates at higher doses were characterised by wide credible intervals. In adults, amphetamines showed a plateau above approximatively 50 mg/day, whereas methylphenidate efficacy increased without evidence of a plateau, possibly due to sparse data. Dose-dependent increases in discontinuation probability due to adverse events were observed for amphetamines (above 25 mg/day for children and 50 mg/day for adults) and methylphenidate (above 50 mg/day for adults, with no clear dose-dependent risk for children). We found no evidence of dose–effect patterns for atomoxetine (in fixed-doses studies) and modafinil. Multiple sensitivity analyses confirmed the robustness of these findings. We found no evidence of intransitivity.

Interpretation Our findings challenge both therapeutic inertia—accepting suboptimal response without further dose titration—and uncritical dose escalation beyond licensed limits, when potential harms outweigh expected benefits. Our findings can inform clinical guidelines and should support shared decision making regarding ADHD medication dosage.

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Introduction

ADHD is a common neurodevelopmental condition, characterised by a persistent and impairing pattern of inattention or hyperactivity–impulsivity that is inconsistent with the developmental stage.[1,2] It affects approximately 5% of children worldwide,[3] and in

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For the **protocol** see https://doi.org/10.17605/OSF.IO/3MY4A

Research in context

Evidence before this study

ADHD medications are part of the multimodal approach to ADHD management. Understanding dose–effect for efficacy and safety is essential to maximise their effectiveness and tolerability. To identify existing evidence synthesis on dose–effects, we searched PubMed on July 17, 2025, for dose–effect meta-analyses focusing on ADHD medications, using the following syntax and search terms, with no language restrictions: ("dose-effect" OR "dose-response") AND (ADHD OR "attention-deficit/hyperactivity disorder" OR "attention deficit hyperactivity disorder"). We found four dose–effect meta-analyses of stimulant and non-stimulant pharmacological interventions in children and adolescents, and in adults with ADHD. These four meta-analyses focused on specific pairwise comparisons against placebo and did not account for indirect evidence arising from other pairwise comparisons. Therefore, there is a need to assess dose–effects across all ADHD medications (stimulants and non-stimulants) simultaneously and across age groups.

Added value of this study

We conducted the first dose–effect network meta-analysis of ADHD medications, including both licensed and unlicensed doses, across age groups. We showed that dose–effect patterns vary across medications and age groups. In children and adolescents, methylphenidate, amphetamines, and guanfacine showed increasing median efficacy up to 45 mg/day, 25 mg/day, and 4 mg/day, respectively, with no evidence of additional benefit at higher doses. In adults, amphetamines showed a plateau above approximatively 50 mg/day. Additionally, we found no evidence that escalation beyond licensed maximum doses improves mean efficacy at the patient-group level, and such increases are typically associated with reduced tolerability.

Implications of all the available evidence

The current dose–effect network meta-analysis presents the most comprehensive evidence to guide dose considerations and inform clinical guidelines at the patient-group level. Overall, our findings indicate that clinicians should avoid suboptimal doses and consider upward titration from minimal doses when symptoms remain insufficiently controlled. Although we found no compelling evidence to support the routine use of doses exceeding FDA-licensed maxima, some individuals with ADHD might require higher-than-licensed doses. In these cases, any potential benefit must be carefully weighed against possible safety concerns identified in long-term observational studies.

40–70% of cases, impairing symptoms persist beyond adolescence, with an estimated prevalence in adults of about 3%.[4] ADHD is associated, on average, with an elevated risk of adverse outcomes, although trajectories vary across individuals. Although treatment does not fully prevent all negative outcomes, access to evidence-based care remains essential to reduce long-term risks such as suicidal behaviours, substance misuse, or accidental injuries.[5,6]

Pharmacotherapy is an important component in the multimodal management strategy of ADHD.[7] Available medications include stimulants, encompassing methylphenidate and amphetamines, and non-stimulants, such as atomoxetine, clonidine, guanfacine, and viloxazine. Given the range of therapeutic options, comparative evidence on their efficacy and tolerability is needed to inform clinical decision making.

A network meta-analysis of 133 double-blind randomised controlled trials (RCTs) evaluating ADHD pharmacological treatments[8] found that, based on clinician-rated ADHD core symptoms at approximately 12 weeks, most medications were superior to placebo in both children and adolescents, and adults. However, amphetamines were also associated with poorer tolerability than placebo in both age groups. Notably, the network meta-analysis did not account for medication dosage, which is a crucial component of treatment effect. In clinical settings, subtherapeutic dosing is not uncommon, especially among children and adolescents,[9–12] potentially leading to reduced clinical benefits and adherence.[11,13] Most clinical guidelines provide limited guidance on how to dose ADHD medications.[14,15] Understanding how efficacy and tolerability vary across doses is therefore essential to inform shared decision making. A dose–effect network meta-analysis builds on standard network meta-analysis methods by modelling the dose–effect relationship across treatments.[16,17] This approach enables the identification of the optimal benefit–harm trade-off across dose ranges, thereby enhancing clinical applicability.

Four dose–effects meta-analyses on ADHD medications have been published.[18–21] Three of them were restricted to children and adolescents[19–21] and examine the patterns of dose–outcome associations of stimulants (methylphenidate, amphetamine),[19] atomoxetine,[20] and viloxazine[21] against placebo. Altogether, these papers indicated a pattern of increasing group-level efficacy with increasing doses until a given point, after which further increases in medication dose were associated with diminished gains in average ADHD symptom reduction or increased average risk of treatment discontinuation due to adverse events (eg, 30 mg/day of methylphenidate, 20 mg/day of amphetamine, 1·2 mg/kg per day of atomoxetine, 400 mg/day of viloxazine). However, these analyses relied on only a subset of the evidence (ie, direct evidence from placebo-controlled trials). Ideally, clinical practice should be informed by the entirety of the evidence, comprising both direct and indirect evidence as estimated in network meta-analyses.

We aimed to investigate these important research gaps by conducting the first dose–effect network meta-analysis across available ADHD pharmacological treatments and age groups, considering also dose beyond the FDA-recommended maximum dose, estimating dose–effect curves for efficacy and tolerability.

Methods

Search strategy and selection criteria

We conducted a systematic review and dose–effect network meta-analysis of double-blind RCTs evaluating oral monotherapy (stimulants and non-stimulants) in individuals aged 5 years and older meeting standardised ADHD criteria. Studies involving genetic syndromes, treatment-resistant populations, or withdrawal-phase designs were excluded.

The protocol was pre-uploaded on OSF and published.[22] For the reporting, we followed the PRISMA extensions for network meta-analyses (appendix p 3).

Eligible RCTs were identified using the MED-ADHD database, a continuously updated repository of double-blind RCTs evaluating pharmacological treatments for ADHD. This database was originally developed by the European ADHD Guidelines Group to conduct the network meta-analysis of ADHD medications.[8] MED-ADHD includes studies retrieved through comprehensive searches of 12 major bibliographic databases (eg, PubMed, Embase, CENTRAL, Web of Science), clinical trial registries, and grey-literature sources (eg, dissertations and trial-registry platforms), without applying language restrictions. The latest update was completed on Feb 17, 2025. The complete search strategy for each database is reported in the appendix (p 5).

We included double-blinded RCTs, with a parallel-group or cross-over design, of pharmacological interventions administered as oral monotherapy for at least 1 consecutive week for the treatment of individuals (aged ≥5 years) with a diagnosis of ADHD, established using operationalised diagnostic criteria (DSM-III or later; equivalent ICD criteria for hyperkinetic disorder were also deemed acceptable). We excluded studies in which participants had a co-occurring genetic syndrome. Eligible medications comprised amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, dexmethylphenidate, extended-release guanfacine, methylphenidate, modafinil, and viloxazine. Trials combining pharmacological treatment with psychotherapy (other than psychoeducation) were excluded. Fixed-dosing and flexible-dosing schedules were included. Fixed-dosing schedule studies were those in which the maximum targeted dose was specified at baseline, with dose reductions permitted only for safety reasons. Flexible doses were used as sensitivity analyses. To be eligible for inclusion, flexible-dose studies had to clearly specify the maximum intended dose at baseline, with dose adjustments permitted for safety or efficacy reasons. The dose in our analysis should be understood as the maximum intended target dose at baseline, rather than the dose received. This analysis preserves randomisation and avoids issues related to selection bias, but might introduce heterogeneity. Any network meta-analysis assumes transitivity (ie, that all treatment in the network could in principle have been compared in a single RCT, and that effect modifiers are similarly distributed across treatment comparisons). We contacted corresponding authors and manufacturers for additional information and data, included grey literature, and translated papers where necessary. More details are reported in the appendix (p 6).

We included summary estimates from each eligible RCT.

Two reviewers working in pairs drawn from the author list (LJ, VP, LF, GFV) independently assessed the risk of bias of retained RCTs using the Cochrane Risk of Bias tool[23] (version 2) in relation to the primary outcome. In case of disagreement between the two reviewers, a third, senior investigator arbitrated (SC). Sensitivity analyses were performed, excluding studies at high risk of bias (appendix pp 337, 350).

See **Online** for appendix

For the **MED-ADHD database** see https://med-adhd.org/

Data analysis

Each step of data collection was conducted independently by pairs drawn from the author list of Cortese and colleagues[8] with updated data collection from MN and LJ with discrepancies resolved by a third senior author (SC). The primary outcome was severity of ADHD core symptoms (total combined [ie, inattentive plus hyperactive or impulsive symptoms]), measured as an endpoint score on a standardised scale filled out by parents, teachers, patients, or clinicians. The prioritisation of scales to include used the following order: ADHD Rating Scale (total score), Swanson, Nolan and Pelham (SNAP) ADHD (total score), Conners rating scale (any version, ADHD total score), or other ADHD scales. We selected the assessment closest to 12 weeks. Efficacy of each medication was estimated using standardised mean difference (SMD). For clinical interpretability, we back-transformed SMDs to mean differences using the median observed SD of the ADHD Rating Scale, the most frequently reported scale. The secondary outcome was tolerability of treatment and all-cause discontinuation (see deviation from protocol), defined as the number of patients leaving the study due to any adverse event or any cause, respectively. Both secondary outcomes were estimated as a risk of dropout for each treatment using estimated odds ratio.

For more on the **European ADHD Guidelines Group** see https://eunethydis.eu/eunethydis-initiatives/european-adhd-guideline-group/

For the primary analysis, only fixed dosing schedules were planned to be included. Treatments with only one or two different dosages examined across trials were excluded from the analysis. For different formulations of the same medication (eg, immediate and extended release for methylphenidate), we used the conversion doses from Farhat and colleagues,[19] converting amphetamine doses as dextroamphetamine-equivalent doses and methylphenidate doses as immediate-release methylphenidate hydrochloride (appendix p 11). When

doses in mg/kg per day were reported, we converted them to mg/day using the mean baseline weight of the study participants. If the baseline weights were missing, the trial was excluded from the analysis. Several sensitivity analyses were prespecified including the exclusion of high risk of bias studies. Additional details are reported in the published protocol.[22]

We conducted a dose–effect network meta-analysis as a three-level hierarchical Bayesian framework, separate for children or adolescents, and adults.[24] To evaluate the plausibility of the transitivity assumption, we compared the distributions of the following ad hoc-specified potential effect modifiers across treatment comparisons:[25] year of study publication, mean age, sex ratio, trial length, types of rater, and ADHD diagnostic criteria.[1,26]

To model the dose–effect relationship for each medication, we used a restricted cubic spline function with three knots placed at the 25th, 50th, and 75th percentiles of the observed dose range. We used minimally informative priors for all variance parameters and flat priors for location parameters (appendix p 391). The model was implemented in R (version 4.3.3) using JAGS through the R2Jags package. We used the posterior distributions to obtain estimates of treatment effects and corresponding 95% credible intervals (95% CrI). The robustness of the findings for the primary outcome was evaluated through sensitivity analyses using alternative knot positions and prior distributions for the between-study variance. Full statistical details, including the hierarchical model, prior specifications, sensitivity analyses, and Markov Chain Monte Carlo convergence diagnostics are provided in the published protocol[22] and in the appendix (p 393). The R code is freely available.

For more information on **R2Jags** see https://github.com/suyusung/r2jags

For the **R code** see https://osf.io/mxrn2/

Due to small sample size, we could not conduct separate analyses for each rater type (ie, parents, teachers, patients, or clinicians). We instead did a single analysis, using an ad-hoc rating hierarchy to prioritise which rater type to include when multiple raters were available from the same study. For children and adolescents, we prioritised clinicians, parents, and then teachers, in this order. For adults, we prioritised clinician assessments over self-reports. Small sample size also prevented separate analyses for children (aged ≥5 to <12 years) and adolescents (aged ≥12 to <18 years); this issue led us to analyse them as a single group (aged <18 years). Separate analyses for lisdexamfetamine and amphetamines were not feasible for the adult analysis. Finally, we were unable to conduct the sensitivity analyses or the tolerability analysis using only fixed-dose studies due to high autocorrelation on some parameters (appendix p 10). We did a post-hoc analysis where we added analyses: (1) using mg/kg per day as dose units for children and adolescents; (2) excluding studies sampling only adolescents; (3) estimating dose-curves for all-cause discontinuations; and (4) incorporating study duration as an effect modifier within a dose–effect network meta-regression model to estimates curves for a 6-week duration (appendix p 394).

For the **interactive tools** see https://mikailnourredine.github.io/ADORMA/

Representatives of ADHD Europe, an association of people with lived experience of ADHD, were involved in the conceptualisation and planning of the study. Details are reported in the appendix (p 395).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

On April 7, 2017, our search identified 9948 potential references for inclusion and our Feb 17, 2025 search identified 5148 references. Of these 15 096 references, 8467 were excluded on the basis of title and abstract suitability. 5862 references were then excluded after a full-text read and of the remaining 767 reports, 164 were included in the systematic review and 113 RCTs (45 in adults and 68 in children and adolescents) were included in the dose-response network meta-analysis (figure 1). The lists of included and excluded RCTs, with reasons for exclusion, are reported in the appendix (pp 13–191). The RCTs included in the analysis recruited a total of 14 138 children or adolescents with a mean age of 11 years (of available data, 9981 [70·6%] were males and 4157 (29·4%) were females) and 11 016 adults with a mean age of 36 years (of available data, 5958 [54·0%] were males and 5056 [46·0%] were females). Data on ethnicity and race were inconsistently reported across RCTs. The characteristics of the included RCTs are presented in the appendix (p 226). The overall risk of bias was classified as high in 20 studies, classified as having some concerns in 43 studies, and classified as low in 50 studies (appendix p 253). Additional data for each analysis, including network plots, dose-distribution plots, and distribution of effect modifiers across comparisons, are available in the appendix (pp 330–394). Interactive tools displaying the estimated efficacy and tolerability of each treatment across doses are available online.

The networks are presented in figure 2. Graphical examination of the distribution of key effect modifiers across treatment comparisons suggested that, in both children or adolescents, and adults, the distribution of effect modifiers was broadly balanced, bearing no strong evidence against the transitivity assumption (appendix pp 358–382). The only notable imbalance was related to age in the analyses in children or adolescents, in which the mean age was slightly higher in the amphetamine versus placebo and versus methylphenidate comparisons (appendix p 358). However, dose–effect patterns remained consistent after excluding adolescent-only trials (appendix pp 389–390).

In relation to the main analysis of efficacy in children or adolescents, we included 18 fixed-dose RCTs (54 arms) comprising 4159 children or adolescents, with a median

age of 10·3 years (IQR 9·5–14·0; 75% boys; appendix p 329). The overall risk of bias was high in four studies, with some concerns in three studies, and low in 11 studies (appendix p 289). Dose–effect curves for each medication are shown in figure 3. The following dose thresholds are the dosage levels where the efficacy was estimated to take its maximum value and should be interpreted as approximate benchmarks. Amphetamine doses were converted to dextroamphetamine-equivalent doses and methylphenidate were presented as immediate-release methylphenidate hydrochloride doses. Dose-specific estimates (SMDs and back-transformed mean differences on the ADHD-Rating Scale) are available in the interactive tool. Methylphenidate reached a peak efficacy of about 45 mg/day (SMD –0·89 [95% CrI –1·18 to –0·60]) with further increase in dose being associated with a reduction of the efficacy, albeit with a high uncertainty (SMD –0·79 [–1·01 to –0·50]). This reduction corresponded to a 1·2-point smaller mean difference on the ADHD-Rating Scale. Amphetamines and guanfacine displayed U-shaped curves. The peak average efficacy was reached at approximately 25 mg/day for amphetamines (SMD –1·06 [95% CrI –1·35 to –0·78]), and 4 mg/day for guanfacine (SMD –0·66 [–0·99 to –0·31]), after which the average SMD increased, suggesting possible reduced efficacy, but with high uncertainty. In fixed-dose RCTs, atomoxetine was evaluated at only three dose levels (20, 45, and 60 mg/day), resulting in limited coverage of the full dose range and an imprecisely estimated dose–effect relationship. Sensitivity analyses exploring alternative model specifications for the fixed-dose studies produced broadly similar findings (appendix pp 332–333). When separating amphetamine from lisdexamfetamine, a dose–effect curve could only be fitted for lisdexamfetamine. The curve for lisdexamfetamine showed a dose–effect relationship up to approximatively 55 mg/day, where the effect reached a plateau with SMD –1·05 (95% CrI –1·40 to –0·69; appendix p 336). Dose–response curves using mg/kg per day and with the dose–effect network meta-regression on study length yielded consistent patterns (appendix pp 384–389).

Adding flexible-dose trials expanded the dataset to 32 RCTs (86 arms), including 6271 children (appendix p 340). The overall risk of bias was high in five studies, with some concerns in eight studies, and low in 19 studies. The shapes of dose–effect curves for amphetamines and guanfacine were similar to those in the fixed-dose analysis, with narrower 95% CrIs. For methylphenidate, the curve up to the FDA-licensed maximum was similar to the fixed-dose results, with narrower 95% CrIs. Inclusion of a single study[27] at 80 mg/day (93 mg/day after dose conversion) extended the range beyond the licensed maximum and suggested a decline in efficacy, albeit with wide uncertainty. For atomoxetine, within the analysed range, doubling the dose was associated with an approximate doubling of the point estimate for treatment effect. A sensitivity analysis excluding studies at high risk of bias confirmed the robustness of these findings on flexible-dose trials (appendix p 337).

Among children and adolescents, the tolerability analysis, which examined discontinuation due to adverse events across 65 RCTs (175 arms, 13 972 children),

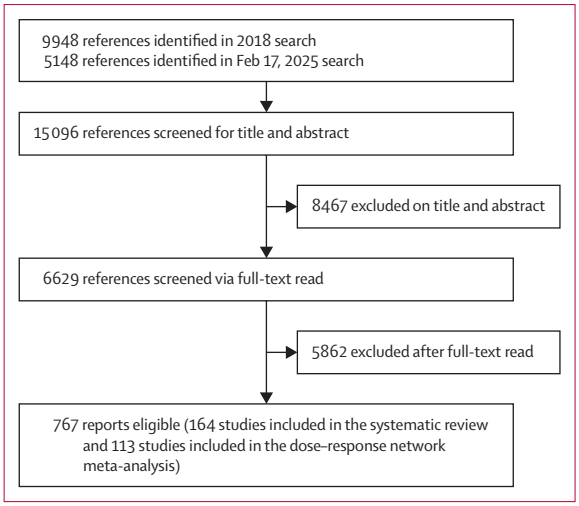

Figure 1: **Study selection**

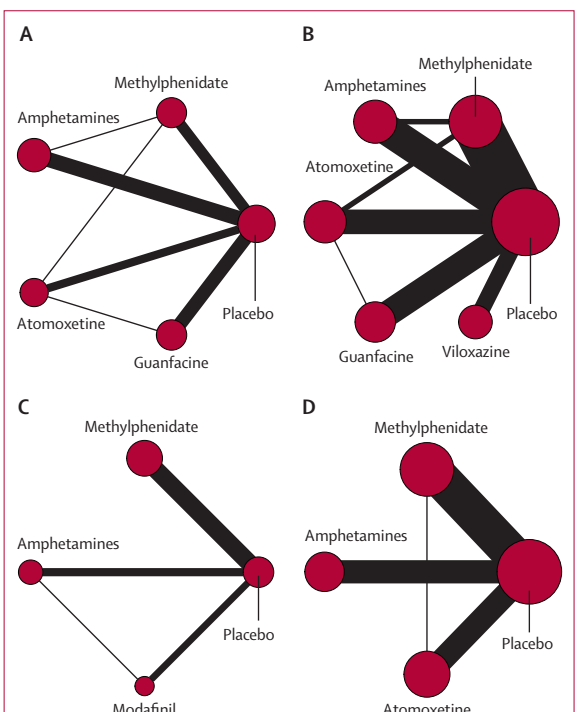

Figure 2: **Network graphics for efficacy (only fixed doses) and tolerability (fixed and flexible doses) analyses**
Efficacy (A) and tolerability (B) in children and adolescents. Efficacy (C) and tolerability (D) in adults. The width of the lines is proportional to the number of trials for each pair of treatments, and the size of each circle is proportional to the number of randomly assigned participants (sample size).

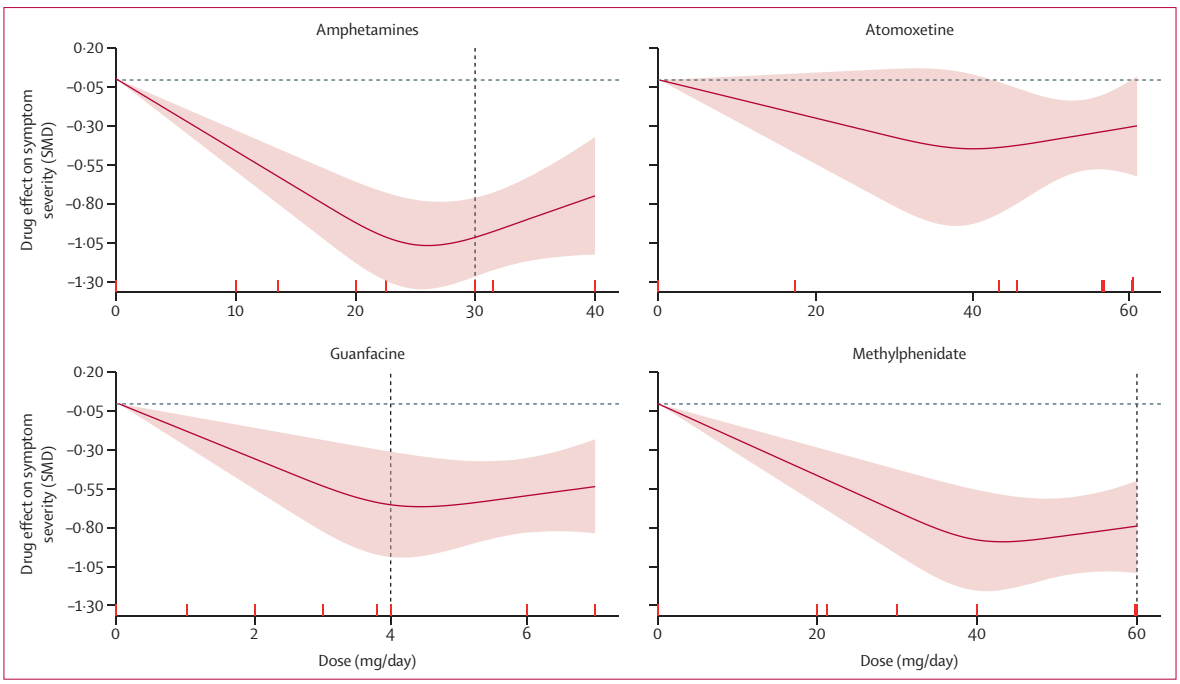

Figure 3: **Dose–effect curves of ADHD medications for children and adolescents**
Data from 19 fixed-dose studies are SMD of symptom severity of each medication versus placebo as a function of the daily dose. The red line depicts the median relative effect of the treatment to the placebo with its 95% credible interval. Red ticks on the x-axis refer to the observed doses. Grey dotted lines indicate the null effect (ie, SMD=0). The black dotted lines represent the maximum doses approved by the Food and Drug Administration (appendix p 329). No black dotted line for atomoxetine is present because its licensed maximum dose in the paediatric population is weight-dependent, and thus a single fixed maximum dose line could not be accurately represented for this medication. Amphetamine doses were converted to dextroamphetamine-equivalent doses and methylphenidate doses were presented as immediate-release methylphenidate hydrochloride doses. SMD=standardised mean difference.

showed distinct dose–risk profiles for each medication (figure 4; appendix p 342). The overall risk of bias was deemed to be high in 12 studies, with some concerns in 20 studies, and low in 33 studies. No clear dose-dependent risk was observed for methylphenidate or atomoxetine. The maximum estimated absolute risk of discontinuation was 2·7% (95% CrI 1·4–5·1) at approximatively 50 mg/day for methylphenidate and 3·6% (1·7–7·1) at approximatively 60 mg/day for atomoxetine, compared with 1·3% (0·9–1·8) for placebo. Increasing methylphenidate dose beyond the FDA-licensed maximum did not raise discontinuation risk, although precision at 90 mg/day was low (median absolute risk 1·7% [95% CrI 0·3–7·4]). Conversely, amphetamines demonstrated a clear linear increase in discontinuation risk, with evidence that risks exceed the placebo risk at doses above approximatively 25 mg/day, which corresponds to its peak of efficacy (figure 3).

Guanfacine displayed a dose-dependent increase in discontinuation risk up to approximatively 4 mg/day, reaching a median risk of 9·8% (95% CrI 4·4–20). Although the average risk appeared to drop after 4 mg/day, the estimate is uncertain, as indicated by the very large 95% CrI. The risk profile for viloxazine remained inconclusive due to the wide credibility interval. Dose–effect network meta-regression models adjusting for study duration yielded consistent patterns (appendix p 387). However, mg/kg per day analyses showed greater uncertainty, probably due to the smaller study subset (n=18 *vs* n=65). Concerning all-causes discontinuation, no clear dose-dependent risk was observed for all medications (appendix p 382).

Among adults, the primary efficacy analysis was based on 11 fixed-dose RCTs (35 arms) including 2450 individuals with a median age of 38·1 years (IQR 35·8–39·9; 59% males). The overall risk of bias was rated high in three studies, with some concerns in six studies, and low in two studies (appendix pp 293–323). Amphetamines reached a plateau at about 50 mg/day, with a SMD of –0·74 (95% CrI –1·26 to –0·20; maximum average FDA licensed dose, 40 mg/day; figure 5). By contrast, the average efficacy of methylphenidate continued to increase across the entire dose range, with diminishing incremental gains approaching 50 mg/day. For modafinil, we found little evidence of a therapeutic effect compared with placebo across all doses; however, estimates were imprecise, with wide credibility intervals. Sensitivity analyses did not materially change these conclusions (appendix pp 348–353).

In the secondary analysis combining fixed and flexible dose studies, the dataset was expanded to 21 RCTs (55 arms, 5025 adults; appendix p 353). The overall risk of bias was high in three studies, with

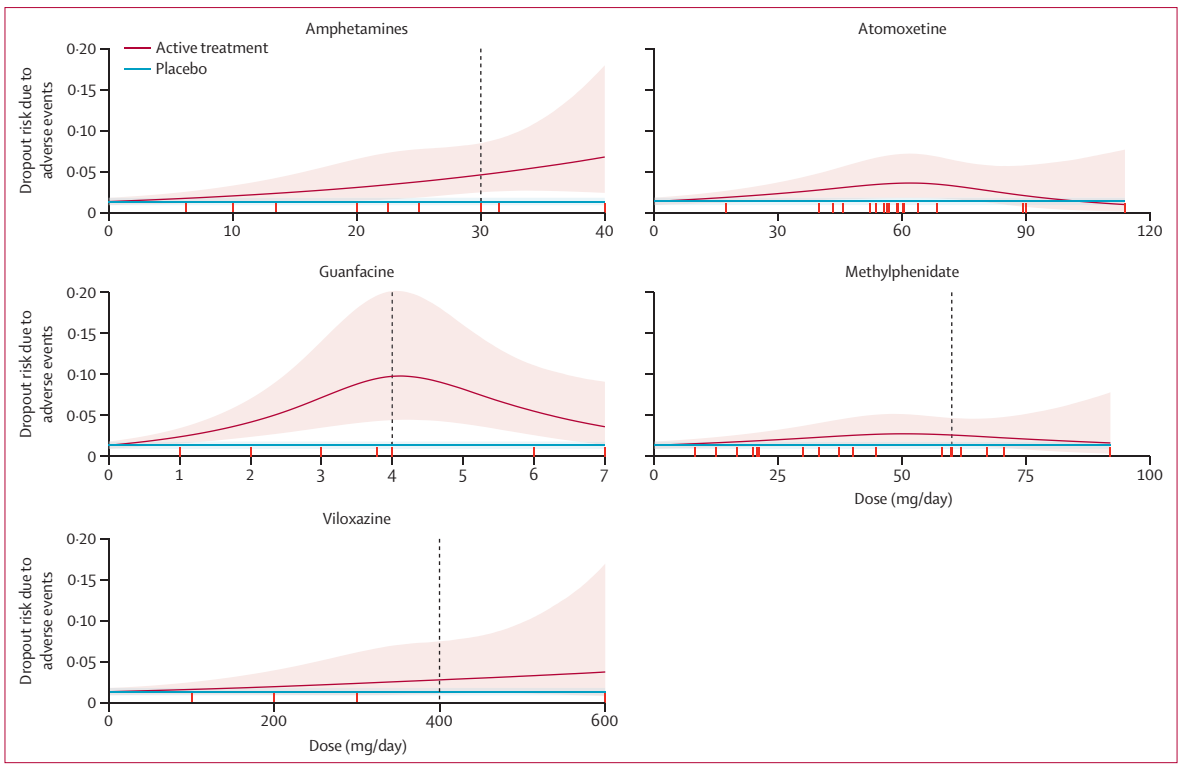

Figure 4: **Dropout proportion curves of ADHD medication for children and adolescents**
Data are from 40 fixed-dose studies and 25 flexible-dose studies. Data are the dropout proportion with each medication as a function of the daily dose. The red line depicts the median proportion dropout of the treatment. The blue line depicts the median proportion dropout of the placebo. The shadow around the curves represents the 95% credible interval. The black dotted lines refer to the maximum doses approved by the Food and Drug Administration (appendix p 329). No black dotted line for atomoxetine is present because its licensed maximum dose in the paediatric population is weight-dependent, and thus a single fixed maximum dose line could not be accurately represented for this medication. Amphetamine doses were converted to dextroamphetamine-equivalent doses and methylphenidate doses were presented as immediate-release methylphenidate hydrochloride doses. SMD=standardised mean difference.

some concerns in 14 studies, and low in four studies (appendix p 325). The dose–effect profiles for amphetamines and methylphenidate remained unchanged compared with the fixed-dose analysis, but with narrower credible intervals. The evidence for both atomoxetine and modafinil was inconclusive, with low estimated effects and large uncertainty. A sensitivity analysis excluding studies with a high risk of bias did not materially change conclusions, although reduced precision was noted, as evidenced by wider 95% CrIs (appendix p 351).

The tolerability analysis in adults included 42 RCTs (104 arms, 10 463 adults; appendix p 354). The overall risk of bias was high in 11 studies, with some concerns in 18 studies, and low in 13 studies. This analysis showed that the risk of discontinuation due to adverse events increased with dose across all medications, although the curve for methylphenidate was steeper (figure 6). The risk of discontinuation related to adverse events for both methylphenidate and amphetamines at doses above approximatively 50 mg/day exceeded the risk in placebo, which was estimated at 2·6% (95% CrI 1·8 to 3·6). At the FDA-licensed maximum dose of methylphenidate (ie, 60 mg/day), the estimated absolute risk of discontinuation due to adverse events was 7·3% (95% CrI 4·3 to 12·0), increasing to 10·0% (5·0 to 19·8) at 90 mg/day, while efficacy improved only modestly, from an SMD of –0·38 (95% CrI –0·62 to –0·17) to –0·52 (95% CrI –0·88 to –0·17; flexible-dose analysis). The risk of dropouts due to adverse events with atomoxetine increased with dose, but the association was weaker and more uncertain for doses below 80 mg/day. Regarding all-cause discontinuation, no clear dose-dependent risk was observed for any of the medications, but uncertainty was high (appendix p 382). The overall shape of the dose–response curves remained consistent even after excluding high-dose regions where data were limited (appendix p 391).

Discussion

To our knowledge, this is the first dose–effect network meta-analysis evaluating the efficacy and tolerability of medications for ADHD in paediatric and adult populations across licensed and unlicensed doses. Similar to previous meta-analyses focused on pairwise effects against placebo, we found a general ceiling effect for efficacy, particularly for stimulants, where dose

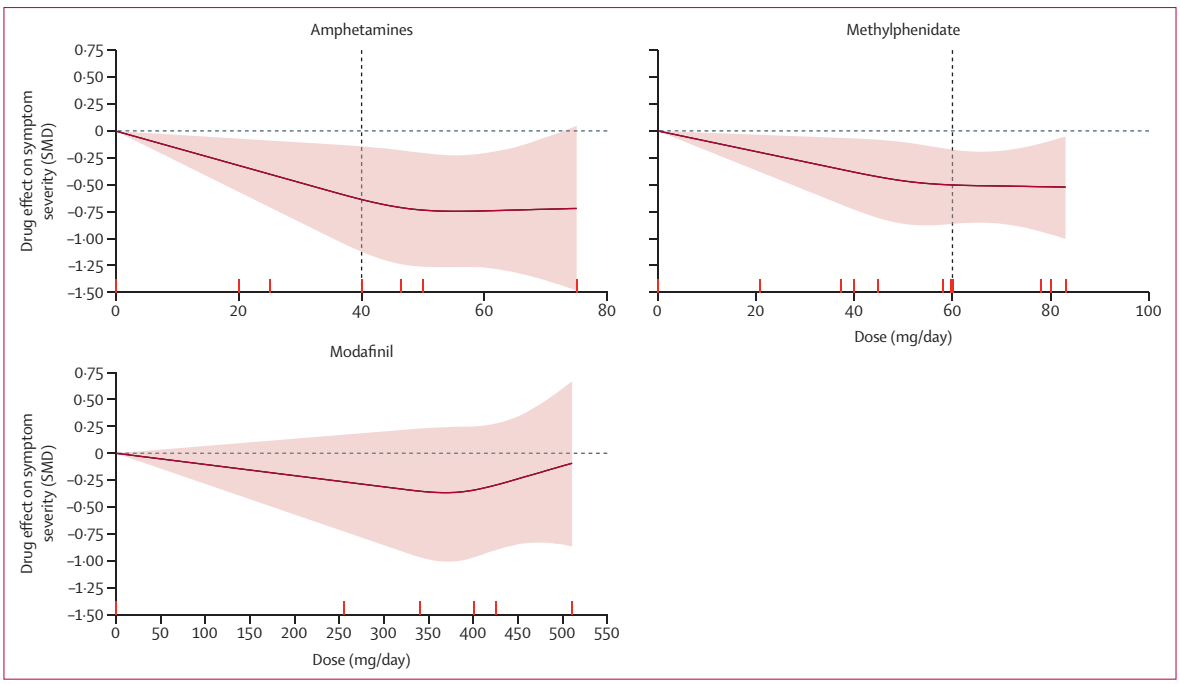

Figure 5: **Dose–effect curves of ADHD medications for adults**
Data from 11 fixed-doses studies are SMD of symptom severity of each medication versus placebo as a function of the daily dose. The red line depicts the median relative effect of the treatment to the placebo with its 95% credible interval. Red ticks on the x-axis refer to the observed doses. Grey dotted lines indicate the null effect (ie, SMD=0). The black dotted lines represent the maximum doses approved by the Food and Drug Administration (appendix p 329). Amphetamine doses were converted to dextroamphetamine-equivalent doses and methylphenidate doses were presented as immediate-release methylphenidate hydochloride doses. SMD=standardised mean difference.

escalation beyond licensed ranges offered diminishing returns or even reduced efficacy alongside poorer tolerability. This benefit–risk profile was broadly consistent across age groups, although dose–effect curves for adults were estimated with higher uncertainty, due to fewer data. Conclusions for high-dose methylphenidate in children should be tempered, as our estimates above the licensed maximum dose were informed by a single study,[27] which targeted 80 mg/day at the start of week 3, while efficacy was assessed at the end of week 3. This short exposure at the highest dose might partly explain the observed pattern, and the finding should be interpreted with caution.

Evidence from real-world studies shows that a substantial proportion of children and adolescents receive low doses of medication without appropriate upward titration.[11,13] This is particularly concerning, as timely and adequate dose adjustment has been associated with improved adherence, probably by facilitating earlier symptom improvement and reinforcing engagement with treatment.[10] Our findings suggest that, in general, clinicians should not hesitate to titrate upward from minimum doses when symptom control remains insufficient. Some authors have advocated off-label use of higher stimulant doses in patients with a partial response.[28] Our study does not support this approach as a general strategy at the patient-group level, given the evidence for a plateau or even decline in efficacy at doses exceeding FDA recommendations. Our results partially align with those of Farhat and colleagues,[18,19] who conducted two dose–effect pairwise meta-analyses of methylphenidate and amphetamines in paediatric[19] and adult populations.[18] In children and adolescents, they observed that gains in efficacy decreased beyond 30 mg of methylphenidate (45 mg in our study) or 20 mg of amphetamines (25 mg in our study). However, their flexible-dose analyses suggested a monotonic improvement with higher stimulant doses, which our fixed-dose and flexible-doses analysis did not corroborate. In adults, in relation to methylphenidate, they found that doses over FDA-licensed doses were superior in efficacy, although the improvement was described as small.[18] Regarding amphetamines, there was no evidence in Farhat and colleagues' study that non-FDA approved doses of amphetamines led to larger reduction of symptomatology, which was also the case in our study. Notably, our study adds important novel insights to existing evidence. We evaluated the full range of ADHD medications rather than limiting the analysis to stimulants, providing a more comprehensive view of dose–effect patterns, and we assessed licensed and unlicensed doses across age groups. Moreover, by conducting a Bayesian dose–effect network meta-analysis, we were able to estimate a-posteriori distribution of treatment effects, an approach that

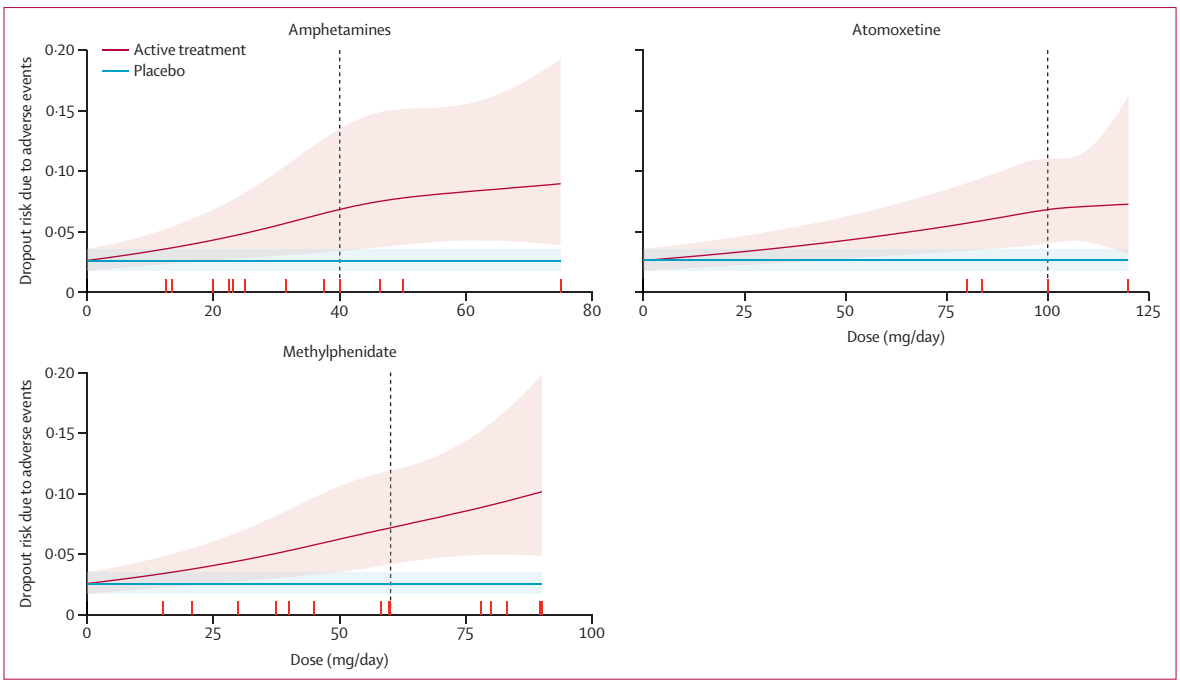

Figure 6: **Dropout proportion curves of ADHD medication for adults**
Data are from 26 fixed-dose studies and 16 flexible-doses studies. Data are the dropout proportion with each medication as a function of the daily dose. The red line depicts the median proportion dropout of the treatment. The blue line depicts the median proportion dropout of the placebo. The shadow around the curves represents the 95% credible interval. Red ticks on the x-axis refer to the observed doses. The black dotted lines refer to the maximum doses approved by the Food and Drug Administration (appendix p 329). Amphetamine doses were converted to dextroamphetamine-equivalent doses and methylphenidate doses were presented as immediate-release methylphenidate hydrochloride doses.

improves interpretability for clinicians and policy makers compared with traditional frequentist analyses.

Our study has limitations. First, only a limited number of doses could be included, particularly in the adult fixed-dose analyses. Second, efficacy was assessed using a heterogeneous set of scales rated by different assessors; however, the distribution of rater types did not appear to differ across comparisons. Third, we could not conduct analyses stratified by sex or ethnicity or race, as subgroup analyses based on these variables were not conducted or reported in most of the included RCTs. Fourth, although we evaluated transitivity across several effect modifiers, others such as impairment severity could not be assessed as they were inconsistently reported across the included RCTs. Fifth, small-study-bias could not be formally assessed. Sixth, our analysis focused on short-term (mean: 7 weeks for adults and 8 weeks for children or adolescents) efficacy and tolerability. Long-term risks must also be considered in clinical decision making. Notably, long-term observational studies have associated high stimulant doses with increased risk of hypertension, particularly for doses in the upper range.[29,30] Specific adverse events could not be assessed due to inconsistent reporting across the included trials. Seventh, the generalisability of our findings is limited by reliance on RCTs that enrol selected populations, which might not fully represent patients seen in routine care according to effect modifier distributions.[31] Eighth, using the maximum intended target dose at baseline preserved randomisation and avoids issues related to selection bias, but might introduce heterogeneity. Finally, our results are valid at the group level but cannot inform decision making at the individual level. Individual variability in response to medication is well documented,[32] and doses higher than the licensed ones might be tolerated and needed to reduce symptom severity in some specific cases. Individuals requiring unusually high doses to achieve symptom relief might also warrant diagnostic reassessment to rule out psychiatric or neurodevelopmental comorbidities (eg, anxiety, mood disorders, sleep problems, autism spectrum disorder). Such comorbidities might influence pharmacological response and mimic ADHD symptoms.[28] In addition to diagnostic reassessment, revisiting patients' expectations regarding treatment outcomes (eg, inappropriate dose escalation following mood-enhancement with stimulants) might also be necessary.[33]

Notwithstanding these caveats, this dose–network meta-analysis provides the most comprehensive aggregate-level evidence synthesis to inform guidelines and shared decision making on dose selection in clinical practice. We deliberately avoided any firm recommendation on the best specific dose for each treatment and for individuals. Our evidence needs to be complemented by personalised considerations for each patient, with cautious dose titration,

as well as implementation of a broader multimodal approach to improve both effectiveness and tolerability of ADHD treatment, ideally in a shared decision-making process.[32]

Contributors

All authors participated in the study design. MN did the statistical analyses supervised by TH and FS. MN and LJ wrote the first draft of the manuscript. All authors revised the manuscript. MN and SC accessed and verified the underlying data. All authors confirm they had full access to all the data in the study and accept final responsibility for the decision to submit for publication.

Declaration of interests

LJ has received travel support from HAC Pharma, InfectoPharm, and has received a mobility grant from the Planiol Foundation. TH was employed by F Hoffmann-La Roche at the time of writing and holds shares in the company. This work was conducted independently, and Roche had no role in the study design, analysis, interpretation, or manuscript preparation. AC received honoraria from Angelini Pharma (digital psychiatry workshops) and Lundbeck Pharma (antidepressant presentations); neither of these activities was related to the current study. VP received travel and fees reimbursement by Medice to attend Eunethydis 2025, and from Infomed not related to the present project. VP is recipient of an NIHR Advanced Fellowship. SC 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, Healthcare Convention and CCM Group team for educational activity on ADHD and has received honoraria from Medice. All other authors declare no competing interests.

Data sharing

Code is available at the OSF repository, aggregate level data from randomised controlled trials included in this study are available upon request at https://med-adhd.org/.

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