The effects of stimulant dose and dosing strategy on treatment outcomes in attention-deficit/hyperactivity disorder in children and adolescents: a meta-analysis.

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**Running title:**

Dose-response meta-analysis of stimulants for pediatric ADHD.

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**ABSTRACT**

Clinical guidelines currently recommend practitioners titrate stimulant medications, i.e., methylphenidate (MPH) and amphetamines (AMP), to the dose that maximizes symptom control without eliciting intolerable adverse events (AEs) when treating attention-deficit/hyperactivity disorder (ADHD) in school-aged children/adolescents. However, robust evidence-base regarding the effects of doses and dosing strategies of stimulants on clinical outcomes in the treatment of children/adolescents with ADHD is currently lacking and stimulants are often underdosed in clinical practice. To address this gap and provide rigorous evidence-base in relation to the dose and dosing strategy of stimulants, we conducted the largest systematic review and dose-response meta-analysis examining change in ADHD symptoms (efficacy), and treatment discontinuations due to AEs (tolerability) and any reason (acceptability). We conducted one-stage random-effects dose-response meta-analyses examining MPH and AMP separately, stratifying trials based on fixed-dose and flexible-dose design. Daily doses of stimulants were converted to MPH- and AMP-equivalent doses by adjusting for different pharmacokinetics across formulations. We also conducted pairwise meta-analyses to provide indirect comparisons between flexible-dose versus fixed-dose trials. Our study included 65 RCTs involving 7 877 children/adolescents. Meta-analyses of fixed-dose trials for both MPH and AMP demonstrated increased efficacy and increased likelihood of discontinuation due to AEs with increasing doses of stimulants. The incremental benefits of stimulants in terms of efficacy decreased beyond 30mg of MPH or 20mg of AMP in fixed-dosed trials. In contrast, meta-analyses of flexible-dose trials for both MPH and AMP demonstrated increased efficacy and reduced likelihood of discontinuations for any reason with increasing stimulant doses. The incremental benefits of stimulants in terms of efficacy remained constant across the FDA-licensed dose range for MPH and AMP in flexible-dose trials. Our results suggest that flexible titration as needed, i.e., considering the presence of ADHD symptoms, and tolerated, i.e., considering the presence of dose-limiting AEs, to higher doses of stimulants is associated with both improved efficacy and acceptability because practitioners can increase/reduce doses based on control of ADHD symptoms/dose-limiting AEs. Although fixed-dose trials that are required by the FDA are valuable to characterize dose-dependency, they may underestimate the true potential benefit of trialing dose-increases of stimulants in clinical practice by not allowing dose adjustment based on response and tolerability. Additional research is required to investigate potential long-term effects of using high doses of stimulants in the clinical practice.

**INTRODUCTION**

Stimulants [1], i.e., methylphenidate (MPH) and amphetamines (AMP), have been recommended as first-line pharmacologic strategy in the treatment of attention-deficit/hyperactivity disorder (ADHD) in school-age children and adolescents [2-5]. This is in line with findings from double-blinded, randomized-controlled trials (RCTs) which have consistently shown that these medications are mostly safe and effective in reducing the severity of ADHD symptoms in the short term [6] with some of the largest effect sizes for any psychotropic medication in child and adolescent psychiatry [7]. Because patients differ in their response to stimulants, optimal doses of these medications are determined individually. Practitioners are advised to start at low doses and titrate up until symptom remission as tolerated to achieve the individual’s optimal dose [2-5].

Despite current recommendations, children/adolescents often receive relatively small daily dosages of stimulants in the community in the US – an average daily dose of ~20-25mg of methylphenidate and ~20 mg of mixed amphetamine salts [8-11] – and in other countries [12], which likely contributes to suboptimal efficacy in ADHD and non-ADHD domains [13], nonadherence [14, 15] and increasing trends of polypharmacy [16-18], e.g., with anti-psychotics, which have unfavorable adverse events (AEs) in youth [19]. The lack of robust evidence-base regarding the effects of doses and dosing strategies of stimulants on clinical outcomes in the treatment of children/adolescents with ADHD likely contributes to underdosing of these medications in the routine clinical practice. Fixed-dose trials are valuable as they enable a strict examination of dose-dependency and are required by the Food and Drug Administration (FDA) to examine efficacy and tolerability of stimulant drugs for ADHD [20]. However, they may obscure the value of titrating up to higher doses as needed and tolerated because individuals are randomly allocated to doses without considering each individual’s response and tolerability to the medication. Although flexible-dose trials do not enable for strict inferences on dose-dependency because individuals within treatment groups are exposed to varying doses, titration as needed and tolerated ensures more appropriate doses for each individual in the trial, which may contribute to increased efficacy and decreased discontinuation rates in comparison to fixed-dose trials.

Importantly, because flexible-dose trials mimic clinical practice, comparing clinical outcomes between fixed-doses and flexible-doses could help clarify the potential added value of flexible titration to the higher doses. In turn, this comparative evidence could inform public health policies and clinical guidelines regarding dosing of stimulants and facilitate proper dose-optimization in clinical practice. To address this research gap and evaluate the effects of stimulant doses on clinical outcomes for ADHD in school-aged children/adolescents (5-18 years old) stratified by dosing regimen (i.e., fixed-doses versus flexible-doses), we performed meta-analyses of aggregated data from double-blinded RCTs of stimulants against placebo.

**METHODS**

We followed PRISMA guidelines. The protocol [21] for this study was pre-registered on PROSPERO (CRD42020161804). Changes to the original protocol were listed, with reasons, in Supplementary Methods 1.

**Eligibility Criteria**

Studies had to be double-blinded RCTs comparing a FDA -licensed stimulant as monotherapy at the maximum FDA-licensed dose against placebo for the acute treatment of children or adolescents (5 years ≤ age < 18 years) with a primary diagnosis of ADHD, according to DSM-III, III-R, IV, IV-TR, or 5 criteria, or equivalent hyperkinetic disorder, according to ICD-9/10 criteria. Studies were required to administer the same dose of stimulant medication for five consecutive days; studies which adopted a daily switch crossover design were eligible provided there were assessments for five trials for each dose [22]. Studies in which participants also received psychotherapy were eligible, but those in which participants received additional medications (beyond stimulants) were excluded due to potential pharmacokinetic interferences. Studies which randomized participants optimized in an open-label phase were not eligible.

**Search Strategy and Study Selection**

We drew on the search used for a network meta-analysis of double blinded RCTs of ADHD medications by the European ADHD Guidelines Group [6] based on 12 electronic databases, the FDA and the European Medicines Agency websites and unpublished information/data systematically gathered from study authors and drug manufacturers. Their search, using the same strategy, was updated on 16th June 2020 to identify additional eligible studies. The detailed search adopted for each database is outlined in Supplementary Methods 2. Importantly, all articles which had their full text screened in the original or updated search were re-examined by two independent reviewers (LCF, EB) to identify potentially eligible studies for the present meta-analysis that were not originally eligible for the network meta-analysis. Conflicts between the two independent reviewers were solved through consultation with a third reviewer (MHB).

**Data Extraction Procedure**

Information from eligible studies was extracted by two independent reviewers (LCF, AL) into an electronic table. Trial (parallel or crossover design, country/ies, industry or academic funding/support, year of publication), participant (mean age and standard deviation, percentage of boys, percentage of individuals who self-identified as white) and treatment (medication administered, daily dose administered, dosing regimen adopted, concomitant psychotherapy, duration of treatment) characteristics were coded.

For fixed-dose trials, i.e., those in which participants were randomly assigned to a pre-specified dose without considering the individual’s response and tolerability to the assigned dose, we extracted the group’s assigned dose. When fixed-dose studies adopted a forced-dose upward titration schedule, i.e., doses were titrated upwards weekly until the target dose was achieved and then maintained, the target dose was extracted. For flexible-dose trials, i.e., those in which patients were randomly assigned to a stimulant arm or placebo and doses were determined individually considering the control of ADHD symptoms and the emergence of intolerable AEs, we extracted maximum dose allowed to enable inferences on the effects of titration as needed and tolerated up to the target dose of the titration schedule. When only doses in mg/kg/day were reported, doses in mg/day were imputed by identifying the average weight for the participants or by imputing average weight according to the United States Centers for Disease Control and Prevention growth charts [23].

**Outcomes**

We examined (1) change in ADHD symptom severity scores on standardized scales (efficacy) and treatment discontinuations due to (2) adverse events (AE) (tolerability) and (3) any reason/total (acceptability). All outcomes were considered in the short-term (time point closest to 12 weeks). For change in ADHD symptom severity scores, the following hierarchies were adopted when pertinent for raters – clinician, teacher and parent – and scales – ADHD Rating Scale (ADHD-RS) [24, 25], Swanson Nolan and Pelham ADHD (SNAP) [26], Conners’ Parent/Teacher Rating Scale (CPRS/CTRS) [27, 28] or any other reported ADHD scale.

**Risk of Bias Assessment**

The Cochrane tool was employed to classify risk of bias (RoB) of the included studies [29]. The following domains were evaluated: randomization process, deviations from intended interventions, missing outcome data, measurement of outcome data and selection of outcome results. Studies were rated at low RoB if all domains were rated at “low” or only two were rated at “some concerns”.

**Calculation of equivalent doses across stimulant formulations**

Doses of different MPH and AMP products were converted to MPH- and AMP-equivalent doses using as reference quantities of d-methylphenidate and d,l-amphetamine in short-acting methylphenidate hydrochloride (Ritalin®/Methylin®) and mixed-amphetamine salts (Adderall®), respectively. Our conversions were made by adjusting for the different pharmacokinetics of each medication, were based on information presented in the FDA Clinical Pharmacology and Biopharmaceutics Reviews, accessed through the FDA-Approved Drugs database [30], and were in line with established procedures in ADHD research [8, 31, 32] and the clinical practice. Table 1 illustrates the conversion factors used for each formulation.

For MPH-equivalents, daily doses of long-acting (Aptensio XR®, Metadate CD®, Metadate ER®, Ritalin LA®, Ritalin SR®, Quillivant XR® and Quillichew ER®) methylphenidate hydrochloride products were extracted at the prescribed doses because long-acting products given once daily provide comparable daily amounts of d-methylphenidate as the short-acting products given at least twice daily [33-36]. However, for osmotic, controlled-release methylphenidate hydrochloride (Concerta®), daily doses were multiplied by 0.83 because 18 mg are considered comparable to 15 mg of short-acting methylphenidate [37]. For short-acting (Focalin®) and long-acting (Focalin XR®) dexmethylphenidate hydrochloride products, which are only composed of d-methylphenidate, daily doses were multiplied by 2 because methylphenidate hydrochloride is a racemic mixture of d,l-methylphenidate [38, 39]. For methylphenidate base (Contempla XR-ODT®) products, daily doses were multiplied by 1.16 as every 10mg of methylphenidate hydrochloride is composed of 8.6 mg (86%) of methylphenidate base [40]. For methylphenidate transdermal system (Daytrana®), daily doses were multiplied by 1.5 because 10mg/9 hours was considered comparable to 18 mg of Concerta® [41].

For AMP-equivalents, daily doses of long-acting (Adderall-XR®, Mydayis®) mixed amphetamine salts products were extracted at the prescribed doses because long-acting products given one time daily provide comparable daily amounts of d,l-amphetamine as the short-acting products given at least twice daily [42, 43]. For amphetamine base (Adzenys ER®, Adzenys XR-ODT®, Dyanavel XR®) products, daily doses were multiplied by 1.6 as 5 mg of mixed amphetamine salts are composed of 3.1 mg (~63%) of amphetamine base [44, 45]. For short-acting (Evekeo®, Evekeo ODT®, Zenzedi®) and long-acting (Dexedrine®) (dextro)amphetamine sulfate products, daily doses were multiplied by 1.16 because 35 mg of mixed-amphetamine salts have comparable amounts of amphetamine base as 30 mg of (dextro)amphetamine sulfate [46]. For lisdexamfetamine dimesylate (Vyvanse®), daily doses were multiplied by 0.45 because 35 mg of mixed-amphetamine salts have comparable amounts of amphetamine base as 75 mg of lisdexamfetamine [46].

**Meta-analytical method**

We conducted one-stage, random-effects dose-response meta-analyses [47, 48] to pool data and estimate the dose-response trends between doses of stimulants (MPH and AMP separately) and each of the clinical outcomes. Fixed-dose and flexible-dose studies were pooled separately. Standardized mean difference (SMD) was used as effect size index for efficacy and relative risk (RR) for tolerability and acceptability. We used different regression models (i.e., linear, quadratic and restricted cubic splines with knots at the 10th, 50th and 90th percentile) and selected the best-fitting one for each outcome according to the smallest values on the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC). When the spline was found best-fitting, we fitted an additional model with knots at the 25th, 50th and 75th percentile and evaluated whether findings remained stable across the different splines [49]. To aid in the interpretation of the dose-response curves, we obtained SMD and RR estimates with 95% confidence intervals (CI) for every 10 mg up to 60 mg of MPH-equivalents, the maximum FDA-licensed dose for MPH, and up to 40 mg of AMP-equivalents, the maximum FDA-licensed dose for mixed amphetamine salts. We performed sensitivity analyses by repeating our procedures after excluding studies with moderate/high RoB, doses determined by weight, crossover design, concomitant psychotherapy, and less than two weeks of duration. We also repeated analyses for efficacy considering ADHD symptom domains (i.e., inattention and hyperactivity/impulsivity separately). All analyses were performed in R with the package ‘dosresmeta’ [50]. The significance threshold for analyses was set at p < .05.

To confirm our findings obtained with the dose-response meta-analyses, we conducted additional pairwise meta-analyses to provide indirect comparative evidence of flexible-dose versus fixed-dose regimens for MPH and AMP as recently implemented in meta-analyses of RCTs of antidepressants [51, 52]. More specifically, we initially calculated summary SMD (efficacy) and odds ratio (OR) (tolerability, acceptability) for fixed-dose studies at 30 mg of MPH-equivalents or below or at 20 mg of AMP-equivalents or below (SMDFix; ORFix) and for flexible-dose studies with titration as needed and tolerated beyond 30 mg of MPH-equivalents or beyond 20 mg of AMP-equivalents (SMDFlex; ORFlex). We then calculated the difference in SMDs (DSMD = SMDFlex – SMDFix) and the ratios of OR (ROR = ORFlex/ORFix), with a DSMD < 0 and a ROR < 1 indicating superiority of the flexible-dose regimen over the fixed-dose one. For MPH, we repeated the analyses considering the threshold for selection of fixed-dose and flexible-dose studies at 40 mg and 50 mg of MPH-equivalents. For AMP, we repeated the analyses considering the threshold for selection of fixed-dose and flexible-dose studies at 30 mg of AMP-equivalents. Data were pooled with random-effects models. For multi-arm studies (e.g., multiple fixed-dose levels of the same medication), we combined the number of participants in the active arm appropriately to avoid double-counting them in summary effect-sizes [53]. Because the DSMD/ROR analyses were across trials and therefore subject to confounding, we compared study-level characteristics of fixed-dose and flexible-dose trials for each compound and outcome separately and re-ran analyses adjusting for covariates in meta-regression if a significant imbalance was detected in regression models [52]. All analyses were performed in R with the package ‘meta’ [54]. The significance threshold for analyses was set at p < .05.

**Data and code availability**

 Data and code are available at OSF (doi.org/10.17605/OSF.IO/XQZE7).

**RESULTS**

Figure S1 illustrates the PRISMA flowchart of the search, and a list of excluded/included references was provided in Supplementary Results 1. Table 2 describes the 65 RCTs involving 7 877 children/adolescents which were included in the present meta-analysis. Table S1 describes a detailed RoB assessment for each study. For MPH, 57 RCTs involving 5 414 children/adolescents were included in the present meta-analysis. The mean age of the sample was 11 years (SD 3), 72% were boys and 76% self-identified as white. There were 157 treatment arms of which 121 (77%) were fixed-dose and 36 (23%) were flexible-dose. The RoB was classified at low for 17 RCTs (30%) and at high for 4 RCTs (7%). For AMP, 14 RCTs involving 2 855 children/adolescents were included in the present meta-analysis. The mean age of the sample was 12 (SD 3), 69% were boys and 74% self-identified as white. There were 42 treatment arms of which 34 (81%) were fixed-dose and 8 (19%) were flexible-dose. The RoB was classified at low for 8 RCTs (57%) and at high for none.

Figure 1 illustrates the best-fitting dose-response curves for MPH-equivalents (panels A to C) and AMP-equivalents (panels D to F) for fixed-dose (solid, blue) and flexible-dose (dashed, red) studies; Table S2 describes the goodness-of-fit measures which were used to guide selection of the optimal dose-response trend for each outcome; Figure S2 illustrates the splines with knots at the 25th, 50th and 75th percentile when the spline was found the best-fitting model; Table S3 describes point SMD and RR with 95% CI for every 10 mg of MPH-equivalents and AMP-equivalents for each outcome.

For MPH, meta-analyses demonstrated a significant dose-response association between MPH-equivalents and efficacy in fixed-dose (Chi-square = 206.48, p < .0001) and flexible-dose (Chi-square = 257.36, p < .0001) studies (Figure 2A). In a fixed-dose regimen, the curve demonstrated incrementally less additional improvements in SMD beyond 30 mg of MPH-equivalents. In a flexible-dose regimen, the curve demonstrated constant increments of 0.18 (95% CI 0.16, 0.20) in SMD for every 10 mg increase in doses of MPH-equivalents across the entire FDA-licensed dose range. Meta-analyses also demonstrated a significant dose-response association between MPH-equivalents and tolerability in fixed-dose (Chi-square = 8.61, p = .003), but not in flexible-dose (Chi-square = 0.08, p = .77), studies (Figure 2B). In a fixed-dose regimen, there were constant increments of 3.59% (95% CI 1.18%, 6.07%) on an exponential scale in the risk of discontinuing treatment due to AEs for every 1 mg increase in doses of MPH-equivalents across the entire FDA-licensed dose range. Lastly, meta-analyses demonstrated a significant dose-response association between MPH-equivalents and acceptability in flexible-dose (Chi-square = 14.25, p = .0002), but not in fixed-dose (Chi-square = 0, p = .98), studies (Figure 2C). In a flexible-dose regimen, there were constant decrements of −0.97% (95% CI −1.48%, −0.47%) on an exponential scale in the risk of discontinuing treatment for any reason for every 1 mg increase in doses of MPH-equivalents across the entire FDA-licensed dose range.

Pairwise meta-analyses corroborated the findings from the dose-response meta-analyses. Figure 2 illustrates the DSMDs and RORs for each outcome for MPH. Meta-analyses demonstrated greater change in ADHD symptoms with flexible titration beyond 30 mg (DSMD = -0.22; 95% CI −0.34, −0.10; p = .0003), 40 mg (DSMD = −0.21; 95% CI −0.34, −0.09; p = .0007) and 50 mg (DSMD = −0.21; 95% CI −0.34, −0.08; p = .002) of MPH-equivalents in comparison to lower fixed doses; decreased risk of dropouts due to AE with flexible titration beyond 30 mg (ROR = 0.34; 95% CI 0.15, 0.79; p = .03) and 40 mg (ROR = 0.33; 95% CI 0.13, 0.86, p = .03), but not 50 mg (ROR = 0.40; 95% CI 0.12, 1.32, p = .18), of MPH-equivalents in comparison to lower fixed doses; decreased risk of dropouts for any reason with flexible titration beyond 30 mg (ROR = 0.42; 95% CI 0.28, 0.64; p < .0001), 40 mg (ROR = 0.43; 95% CI 0.29, 0.62; p < .0001) and 50 mg (ROR = 0.54; 95% CI 0.31, 0.94; p = .01) of MPH-equivalents in comparison to lower fixed doses. Table S4 describes study-level characteristics of fixed-dose and flexible-dose trials and Figure S3 illustrates the DSMDs and RORs after adjustment for covariates for each outcome for MPH. For efficacy, the DSMDs favored flexible-dose studies further. For acceptability, while ROR point estimates were stable, there was marked decrease in precision and results were no longer significant for flexible titration beyond 40 mg and 50 mg over lower fixed doses.

For AMP, meta-analyses demonstrated a significant dose-response association between AMP-equivalents and efficacy in fixed-dose (Chi-square = 82.17, p < .0001) and flexible-dose (Chi-square = 102.70, p < .0001) studies (Figure 2D). In a fixed-dose regimen, the curve approached a plateau beyond 20 mg of AMP-equivalents. In a flexible-dose regimen, the curve resembled a straight line with constant increments of 0.42 (95% CI 0.34, 0.51) in SMD for every 10 mg increase in doses of AMP-equivalents across the entire FDA-licensed dose range. Meta-analyses also demonstrated a significant dose-response association between AMP-equivalents and tolerability in fixed-dose (Chi-square = 7.69, p = .005) and flexible-dose (Chi-square = 4.35, p = .03) studies (Figure 2E). In a fixed-dose regimen, there were constant increments of 3.34% (95% CI 0.97%, 5.78%) on an exponential scale in the risk of discontinuing treatment due to AEs for every 1 mg increase in doses of AMP-equivalents across the entire FDA-licensed dose range. Likewise, in a flexible-dose regimen there were constant increments of 2.63% (95% CI 0.16%, 5.18%) on an exponential scale in the risk of discontinuing treatment due to AEs for every 1 mg increase in doses of AMP-equivalents across the entire FDA-licensed dose range. Lastly, meta-analyses demonstrated a significant dose-response association between AMP-equivalents and acceptability in flexible-dose (Chi-square = 3.87, p = .049), but not in fixed-dose (Chi-square = 0, p = .92), studies (Figure 2F). In a flexible-dose regimen, there were constant decrements of −1.39% (95% CI −2.75%, −0.01%) on an exponential scale in the risk of discontinuing treatment for any reason for every 1 mg increase in doses of AMP-equivalents across the entire FDA-licensed dose range.

Pairwise meta-analyses corroborated the findings from the dose-response meta-analyses. Figure 2 illustrates the DSMDs and RORs for each outcome for AMP. Meta-analyses demonstrated greater change in ADHD symptoms with flexible-titration beyond 20 mg (DSMD = -0.50; 95% CI −0.93, −0.07; p = .01) and 30 mg (DSMD = -0.59; 95% CI −0.99, −0.18; p = .002) of AMP-equivalents in comparison to lower fixed-doses; no significant differences in risk of dropouts due to AEs with flexible-titration beyond 20 mg (ROR = 1.32; 95% CI 0.38, 4.51; p = .81) and 30 mg (ROR = 0.96; 95% CI 0.29, 3.15; p = .73) of AMP-equivalents in comparison to lower fixed-doses; decreased risk of dropouts for any reason with flexible-titration beyond 20 mg (ROR = 0.54; 95% CI 0.31, 0.93; p = .04) and 30 mg (ROR = 0.43; 95% CI 0.25, 0.76; p = .003) of AMP-equivalents in comparison to lower fixed-doses. Table S5 describes the study-level characteristics of fixed-dose and flexible-dose trials for each outcome for AMP. There were no significant imbalances between fixed-dose and flexible-dose studies for each outcome.

Figure S4 illustrates dose-response curves for ADHD symptom domains – there were not large differences in the dose effects of MPH-equivalents and AMP-equivalents on inattention and hyperactivity/impulsivity symptoms. Figure S5 to S9 illustrate the dose-response curves for analyses after excluding studies with moderate/high RoB, doses determined by weight, crossover design, concomitant psychotherapy and less than two weeks of duration. Findings remained stable across all sensitivity analyses.

**DISCUSSION**

We conducted the first meta-analysis [55] evaluating the effects of doses of MPH and AMP on clinical outcomes for children and adolescents treated for ADHD. Fixed-dose trials are invaluable because they enable careful examinations of dose-dependency and provide important information regarding efficacy and safety of new medications in the drug development process [20]. However, flexible-dose trials relate more closely to the clinical practice and their procedures (individualized decisions to increase/decrease doses considering the patients’ ADHD symptom severity and intolerable AEs) might contribute to maximize the benefits and diminish the detriments of the higher doses. In our analyses, we found significant dose-response associations between stimulant doses and efficacy and tolerability in fixed-dose trials for both MPH and AMP. More specifically, we found increased reductions in ADHD symptoms and increased likelihood of discontinuation due to AEs with increasing doses of stimulants. However, the added gains in efficacy decreased beyond 30mg of MPH or 20mg of AMP in fixed-dosed trials. In contrast, we found significant dose-response associations between stimulant doses and efficacy and acceptability in flexible-dose trials for both MPH and AMP. More specifically, we found increased reductions in ADHD symptoms and reduced likelihood of discontinuations for any reason with increasing stimulant doses. The added gains in efficacy remained constant across the FDA-licensed dose range for MPH and AMP in flexible-dose trials. Taken together, our findings from fixed-dose and flexible-dose studies provided compelling evidence in favor of titrating doses up to the maximum FDA-licensed doses unless ADHD symptom severity diminishes to the point where there is little room for further improvement, or dose-limiting AEs appear, in the management of ADHD in children/adolescents.

Clinical practice guidelines recommend flexible titration of stimulants in the management of ADHD in children/adolescents [2-5], but evidence from community treated children/adolescents indicate that a relatively large proportion of children/adolescents (30%-40%) do not undergo dose escalation in routine practice in the US [9, 56], and when they do upwards titration often stops at relatively low doses [9]. Although individual fixed-dose RCTs [57-60] had initially suggested that higher doses of stimulants were associated with increased reductions in the severity of ADHD symptoms in children/adolescents, our findings demonstrate that even larger reductions in ADHD symptoms can be achieved if the decision to use higher doses is individualized considering the severity of ADHD symptoms and dose-limiting AEs. Notably, our flexible-dose curves demonstrated constant increments in SMD of ~0.2 and ~0.5 for every 10 mg of MPH-equivalents and AMP-equivalents across the entire FDA licensed dose for methylphenidate and mixed amphetamine salts, respectively, and this finding was strikingly replicated in our pairwise meta-analyses. Hence, our study provides definitive evidence that suboptimal treatment of ADHD is administered when practitioners do not escalate doses, or stop escalation before maximum FDA-licensed doses, unless ADHD symptom severity diminishes to the point where there is little room for further improvement, or dose-limiting AEs appear.

Child and family preferences and concerns with AEs at higher doses are of crucial importance when escalating doses in routine clinical practice and must be considered. Indeed, surveys have shown some practitioners guide optimization according to child/family preferences [61] and psychiatrists have reported that the most common reason for not using a rigorous titration schedule was that family members declined further dose escalation once some improvement in the child’s behavior was observed [8]. Evidence-based communication with families could help address their concerns regarding flexible titration to maximum FDA-licensed doses as needed, i.e., considering the presence of ADHD symptoms, and tolerated, i.e., considering the presence of dose-limiting AEs, and our meta-analyses provide important evidence which should be used to inform these conversations. More specifically, our meta-analyses demonstrated that increments in doses of either MPH or AMP were associated with increased risk of treatment discontinuation due to AEs in a fixed-dose regimen. However, we note some of the short-term stimulant-related AEs, e.g., sleep disturbances and appetite change, can often be managed [62] and doses can be reduced if AEs become intolerable in flexible titration to avoid discontinuation. Indeed, our findings demonstrated flexible titration mitigated the risks of discontinuing treatment due to AEs: for methylphenidate, the association between MPH-equivalents and decreased tolerability was non-significant in a flexible-dose design; for AMP, flexible titration beyond 20 mg and 30 mg of AMP-equivalents was not significantly associated with decreased tolerability over lower fixed-doses. By contrast, our meta-analyses provide evidence that flexible titration up to maximum FDA-licensed doses as needed and tolerated is in fact associated with a decreased risk of treatment discontinuation because the added efficacy obtained with flexible titration is associated with a decreased likelihood of discontinuing stimulant treatment due to perceived lack of efficacy in the short-term [63].

We note that our study was based on aggregated data (i.e., means and standard deviations, number of dropouts) reported in RCTs and was not designed to consider individual-level characteristics (e.g., age, weight, comorbidities and even genetic background) that could contribute to different patterns of dose-response across individuals. Consequently, our study is not suitable to inform predictions of optimal doses or expected benefits (efficacy) and risks (tolerability; acceptability) for different doses at the individual level for each patient, which can only be addressed considering individual-level data. We stress that the average treatment effects we found in favor of flexible titration likely indicate there are individuals who are going to experience substantially larger benefits with higher doses (e.g., 54 or 72 mg of methylphenidate osmotic, controlled-release). In fact, extrapolation of our dose-response curves beyond FDA-licensed doses would suggest there are individuals who might even experience continued benefits beyond FDA-licensed doses, although this consideration is not based on available evidence and requires direct examination in future research. Regardless, our data does not support inferences on predicted optimal doses for a given patient. Instead, our study represents the most rigorous evidence applicable at the group level to provide general guidance and raise awareness in favor of careful and full dose-optimization in the management of ADHD in children and adolescents.

Although practitioners are faced with the issue of starting a pharmacological treatment and choosing a dosing strategy, and our meta-analysis provides the most rigorous evidence in favor of full flexible titration to maximum FDA-licensed doses as needed and tolerated, we note that the treatment of ADHD in children/adolescents is a long-term intervention. Unfortunately, our data are limited to the short-term and as such they cannot inform on important questions of the long-term treatment of children/adolescents with ADHD. First, dose adjustments might be required in the maintenance phase of stimulant treatment. There likely exists a strong correlation between end-of-titration optimal dose and maintenance dose [64], but it is possible that some children/adolescents may need dose increments which may fall beyond the FDA-licensed dose range if maximum doses were considered optimal during titration; the effects of using doses beyond the FDA-licensed range are unclear and require direct examination by future research. Second, some AEs which might only be present in the long-term may be associated with cumulative stimulant doses. For instance, the MTA follow-up study recently reported for the first time a significant association between stimulant use over development and decreased adult height, which could be due to higher cumulative stimulant doses in the MTA sample in comparison to those from studies reporting negative findings [65]. Although the impact on adult height is debatable considering the burden of ADHD, other long-term AEs such as increments in heart rate [66] could also be associated with cumulative stimulant doses and could be particularly burdensome. The cumulative effects of stimulant doses also warrant direct examination by future research.

Our study has limitations. We note we only considered change in ADHD symptoms as the efficacy outcome rather than functional outcomes [67] or associated psychopathology, e.g., emotional dysregulation [68, 69], which reflects the availability of outcomes in individual RCTs. In fact, the majority of RCTs for ADHD still use ADHD symptoms as the primary outcome [67], which limits our ability to examine other outcomes for efficacy. Future research should consider examining dose-response curves of stimulants for functional outcomes and accompanying psychopathology when more data is available. However, we note most of the current clinical practice guidelines still recommend dose-optimization against ADHD symptoms rather than functioning or accompanying psychopathology [2-4], with a few notable exceptions [5]. Besides, our definition of tolerability only considered dropouts due to AEs; a detailed examination of individual AEs should be addressed n in future research. We also note stimulant medications have differing pharmacokinetic properties which may affect the efficacy and tolerability even if given in the same total daily dose. We did not investigate dose-response associations considering doses by weight (mg/kg/day) because a small number of studies adopted such dosing design, but future studies could examine this question if more data are available. Also, our DSMD/ROR analyses could be subject to residual confounding due to unmeasured variables. Lastly, children who participate in RCTs may be more motivated to receive stimulants or, alternatively, their parents may be more willing to accept higher doses than in community care. This difference may affect the generalizability of our results.

 Notwithstanding these caveats, the present meta-analysis provides evidence demonstrating the importance of dose-optimization across the entire FDA-licensed dose range unless ADHD symptoms severity diminishes to the point where there is little room for further improvement, or dose-limiting AEs appear, in the management of ADHD in children/adolescents. Clear, evidence-based communication with families about the importance of escalating doses could help decrease their concerns regarding higher doses.

**Conflict of interest.**

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**Author contributions.**

LCF, GVP and MHB conceived the idea. LCF, EB, AL, SC acquired the data. LCF, JF, VJAQ, AL, MHB analyzed the data. LCF, GVP, MHB wrote the first draft. SC provided key expert comments on the analyses and first draft. All authors contributed to writing and editing of the final draft.

**Supplementary information**

Supplementary information is available at MP’s website

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**FIGURES**

**Figure 1. Dose-response curves for methylphenidate (panels A to C) and amphetamine (panels D to F) products.** Curves represent average effect sizes for efficacy (panels A and D), tolerability (panels B and E) and acceptability (panels C and F) and equivalent doses for methylphenidate (MPH) and amphetamine (AMP) for fixed-dose (solid, blue) and flexible-dose (dashed, red) studies. Point estimates are represented with 95% confidence intervals for every 10 mg of MPH- or AMP-equivalents. The arrow in the Y-axis represents the direction towards added benefits.

**Figure 2. Indirect comparisons of flexible-dose versus low fixed-dose studies**. Forest plots illustrate differences in standardized mean difference (DSMDs) of efficacy and ratio of odds ratio (ROR) of tolerability and acceptability with 95% confidence intervals (CI) for methylphenidate (MPH) and amphetamine (AMP) of flexible-dose studies over smaller fixed-doses. For MPH, 30 mg, 40 mg and 50 mg of MPH-equivalents were used as threshold. For AMP, 20 mg and 30 mg of AMP-equivalents were used as threshold