**Treatment Outcomes With Licensed and Unlicensed Stimulant Doses for Adults With Attention-Deficit/Hyperactivity Disorder**

**A Systematic Review and Meta-Analysis**

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**KEY POINTS**

**Question:** Are unlicensed doses of stimulants associated with positive treatment outcomes in adults with attention-deficit/hyperactivity disorder (ADHD)?

**Findings:** In this meta-analysis of averages, unlicensed doses of stimulants were associated with small, possibly non-clinically meaningful additional reductions of ADHD symptoms and increased risk of treatment discontinuation due to adverse events in relation to licensed doses of these medications.

**Meaning:** Based on averages, unlicensed doses may not have positive risk-benefits for adults with ADHD; practitioners should generally consider unlicensed doses cautiously, but may trial them in individual cases, as average associations will not generalize to every patient.

**ABSTRACT**

**Importance:** Stimulants (methylphenidate, amphetamines) are often prescribed at unlicensed doses for adults with attention-deficit/hyperactivity disorder (ADHD). Whether dose escalation beyond FDA recommendations is associated with positive risk-benefits is unclear.

**Objective:** To investigate the impact, on averages, of stimulant doses on treatment outcomes in adults with ADHD and to determine, based on averages, whether unlicensed doses are associated with positive risk-benefits compared to licensed doses.

**Data Sources:** Twelve databases including published (PubMed, Cochrane Library, Embase, Web of Sciences) and unpublished (ClinicalTrials.gov) literature up to February 22, 2023, without language restrictions.

**Study Selection:** Two researchers independently screened records to identify double-blinded randomized-controlled trials of stimulants against placebo in adults (≥ 18 years) with ADHD.

**Data Extraction and Synthesis:** Aggregate data were extracted and synthesized in random-effects dose-response meta-analyses and network meta-analyses.

**Main Outcome Measures:** Change in ADHD symptoms and discontinuations due to adverse events.

**Results:** 47 randomized-controlled trials (7,714 participants) were included. For methylphenidate, dose-response curves indicated additional reductions of symptoms with increments in doses, but the gains were progressively smaller and accompanied by continued additional risk of adverse events dropouts. Network meta-analyses showed that unlicensed doses were associated with greater reductions of symptoms compared to licensed doses (standardized mean difference [SMD] -0.23; 95% confidence interval [CI] -0.44, -0.02; very low certainty of evidence), but the additional gain was small and accompanied by increased risk of adverse event dropouts (odds ratio [OR] 2.02; 95% CI 1.19, 3.43; moderate). For amphetamines, dose-response curve approached a plateau and increments in doses did not indicate additional reductions of symptoms, but there were continued increments in the risk of adverse event dropouts. Network meta-analysis did not identify differences between unlicensed and licensed doses for reductions of symptoms (SMD -0.08; 95% CI -0.24, 0.08; very low).

**Conclusions and Relevance:** Based on averages,unlicensed doses may not have positive risk-benefits in relation to licensed doses for adults with ADHD. In general, practitioners should consider unlicensed doses cautiously. However, the findings are averages and will not generalize to every patient. Practitioners may trial unlicensed doses if needed and tolerated but should be aware that there may not be large gains in the patients’ response to the medication with those further increments in dose.

**INTRODUCTION**

Stimulants (methylphenidate and amphetamines) are recommended in clinical practice guidelines (CPGs)1-3 for the treatment of adults with attention-deficit/hyperactivity disorder (ADHD), a common psychiatric condition4,5 that has been associated with criminality,6 increased mortality7 and substantial financial costs.8 Because there is considerable variability in how patients respond to stimulants, practitioners are advised to adopt escalating-dose, stepwise-titration to identify optimal doses that ensure maximal reductions of symptoms, improvement in functioning and acceptable tolerability.9–12

Based on currently available evidence, practitioners are unable to predict the optimal dose for a given patient *a priori* without trialing doses, as needed and tolerated, sequentially. While there is consensus that stimulants should be started at low doses, there is little agreement on the maximum doses at which escalation should stop, with CPGs generally recommending levels that are higher than those licensed by regulatory agencies such as the US Food and Drug Administration (FDA). For instance, while the FDA recommends a maximum of 60 milligrams per day (mg/d) for most formulations of methylphenidate, CPGs1-3 generally recommend doses up to 100 mg/d.

Whether stimulant dose escalation beyond FDA recommendations is associated with positive risk-benefits is unclear. Although an analysis at the level of the individual is required for the identification of personalized trade-offs, an examination based on averages may be useful to inform expectations about such risk-benefits in the absence of evidence-based personalized information. Indeed, recommendations from CPGs1-3 are based on average associations13 to inform practitioners about expected outcomes, which may or not apply to individuals in routine clinical practice.

Current recommendations from CPGs about stimulant dosing for adults are based on the observation that flexible-dose randomized-controlled trials (RCTs) allowing titration to higher doses14,15 showed the largest effect sizes across RCTs.16 However, since then, large fixed-dose RCTs have not confirmed a dose-response relationship between stimulants and reductions of symptoms.17-19 Given these mixed findings, rigorous systematic reviews and meta-analyses are needed to inform guideline development, evidence-based communications with patients and decision making.20

This study aimed at filling this gap. We identified RCTs of stimulants against placebo in adults with ADHD and conducted dose-response meta-analyses with fixed-dose RCTs to evaluate the associations, based on averages, between doses and treatment outcomes. Fixed-dose RCTs enable strict examination of dose-dependency.21 However, they may underestimate reductions of symptoms and inflate drop-out rates at the higher doses as participants who are unable to tolerate a given dosage are removed rather than given a lower dose.22 Flexible-dose RCTs are more closely related to real-world practices and may be particularly appropriate to investigate the benefits of escalation to higher doses.23 Besides, treatment decisions such as the prescription of stimulants at licensed or unlicensed doses are dichotomous, which is not captured by dose-response meta-analyses that assess doses continuously. Therefore, we also conducted network meta-analyses (NMAs) with fixed-dose and flexible-dose RCTs to estimate the comparative outcomes of stimulants at unlicensed doses in relation to licensed doses. NMAs allowed us to extend beyond the direct evidence (from fixed-dose RCTs with stimulant arms at licensed and unlicensed doses) and incorporate indirect evidence (from RCTs of any dosing design with stimulant arms at any dose against placebo) in network estimates, ensuring increased statistical power and precision of the resulting estimates.24

**METHODS**

 We followed the Cochrane Handbook25 and PRISMA26 (eMethods 1) and pre-registered the protocol (PROSPERO CRD42020161804) (eMethods 2).

**Data sources**

We drew on a database of RCTs of ADHD medications,13 collated through searches in 12 electronic databases including published (e.g., PubMed, the Cochrane Central Register of Controlled Trials, Embase, Web of Science Core Collection) and unpublished (e.g., ClinicalTrials.gov) literature, from inception to February 22nd, 2023 (eMethods 3), without language restrictions.

**Study selection**

Two researchers independently screened titles/abstracts and then conducted full-text assessment of selected records to confirm eligibility. Any discrepancies were discussed with a third senior researcher. We included double-blinded placebo-controlled RCTs that examined methylphenidate or amphetamines as monotherapy for at least one week in adults (≥ 18 years) with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (eMethods 4).

**Data extraction**

Aggregate data were extracted independently by two investigators (eMethods 5). For fixed-dose RCTs, we extracted the group’s assigned dose in mg/d. For flexible-dose RCTs, we extracted the maximum dose in the titration schedule in mg/d. When doses were determined by weight (e.g., 1 mg/kg/d), we calculated the doses in mg/d considering the sample’s average weight. We also coded whether doses were within (licensed) or beyond (unlicensed) the FDA recommended range for each medication (eTable 1). Lastly, we converted doses of methylphenidate and amphetamines formulations in equivalent doses considering immediate-release methylphenidate hydrochloride and mixed amphetamine salts as the reference medications, respectively (eTable 1, eMethods 6).

**Outcomes**

The primary outcome was change in ADHD symptoms from baseline to endpoint. When data from multiple informants were available, we preferred observer/clinician reports. When data from multiple rating scales were available, we preferred the ADHD rating scale (ADHD-RS),27 the Conners Adult ADHD Rating Scale (CAARS)28 or any other rating scale, in that order. We considered results from intention-to-treat (ITT) analyses, using the method adopted by each study to handle missing data. However, we also considered data from participants who completed the study (modified ITT) if those were the only data reported. Secondary outcomes were discontinuation rates due to adverse events (tolerability) and any reason (acceptability).

**Data synthesis**

We calculated standardized mean difference (SMD) (change in ADHD symptoms) and odds ratio (OR) (tolerability, acceptability) with 95% confidence intervals (CI). We conducted analyses for methylphenidate and amphetamines separately.

We conducted one-stage random-effects dose-response meta-analyses29 using restricted cubic splines with knots at the 10th, 50th and 90th percentiles30 or log-linear/linear regression to model the dose-response associations. The log-linear/linear function was only chosen if the second coefficient of the spline was not significantly different from zero.31 We converted SMD and OR to change in ADHD-RS values and number needed to harm (NNH), respectively, because those are clinically interpretable measures (eMethods 7). For change in ADHD symptoms, we also estimated the 50% and 95% effective doses (ED50, ED95), which represent the mean dose that is associated with 50% and 95% of the maximum change in ADHD symptoms compared to placebo, respectively.32

We then conducted frequentist random-effects NMAs33 to compare placebo, licensed and unlicensed doses of stimulants. We evaluated the plausibility of the transitivity assumption by comparing the distribution of clinical and methodological characteristics across comparisons (eMethods 8). We assumed common heterogeneity variance $τ^{2}$ across comparisons.

We quantified heterogeneity in dose-response meta-analyses with the variance partition coefficient (VPC)29 and in NMAs by comparing $τ$2 with its empirical distribution.34,35 In NMAs, we assessed incoherence with global and local tests.36,37

We assessed risk of bias of RCTs for each outcome with the Cochrane risk of bias tool-2 (eMethods 9).38 We plotted contour-enhanced funnel plots39 for the placebo-controlled comparisons to evaluate publication bias if more than ten studies were available. We assessed the certainty of findings from the NMAs with the Confidence in Network Meta-Analysis (CINeMA) framework40,41 (eMethods 9).

The robustness of our findings was examined in numerous sensitivity analyses for both dose-response meta-analyses and NMAs (eMethods 10).

All analyses were conducted in R (version 4.2.2) with packages *dosresmeta*31(version 2.0.1), *meta*42 (version 6.2-1) and *netmeta*43(version 2.8-0).

**RESULTS**

**Study selection and characteristics**

 Of the initial 14,331 records retrieved through literature searches and screened, 47 RCTs (29 methylphenidate; 18 amphetamines) were included (Figure 1) (eResults 1). These trials comprised 7,714 participants (5,125 methylphenidate; 2,589 amphetamines) with a mean age of 35 (SD 11), of whom 4,204 (56% of those with available data) were males and 5,153 (87% of those with available data) self-identified as White (eTable 2). Most RCTs recruited participants diagnosed with DSM-IV criteria (40, 85%) and were exclusively conducted in the United States (32, 68%) (eTable 2). Additionally, most RCTs adopted a flexible-dose design (27, 57%) (eTable 3), had parallel arms (29, 62%) and were conducted in the short-term (median duration 4.5 weeks, IQR [3-6]) (eTable 2). Eight (18.2%) RCTs were rated at high risk of bias, 14 (31.8%) at low risk of bias and 22 (50%) at some concerns of risk of bias for the primary outcome (eResults 2).

**Methylphenidate**

*Change in ADHD symptoms*

The dose-response curve based on eight fixed-dose RCTs and 18 stimulant arms (dose range 15, 82.5 mg/d) indicated that increments in dose were associated with additional reductions of symptoms throughout the entire dose range for which data were available. However, improvements were incrementally smaller beyond 35-40 mg/d (Figure 2A; Table 1, which also reports change in ADHD-RS values). Consistently, the ED50 was estimated at 25 mg/d while the ED95 was estimated at 72.5 mg/d.

NMA corroborated that unlicensed doses were associated with larger reductions of symptoms in relation to licensed doses, but the incremental benefit was small (26 studies; SMD -0.23; 95% CI -0.44, -0.02; P = .03; very low certainty of evidence) (Figure 3A; eFigure 1,2; eTable 4).

*Tolerability*

The dose-response curve based on seven fixed-dose RCTs and 17 stimulant arms (dose range 15, 82.5 mg/d) indicated a log-linear association with increments of 2.23% (95% CI 1.11%, 3.35%) on an exponential scale in the risk of dropping out due to adverse events for every 1 mg/d increase throughout the entire dose range for which data were available (Figure 2B; Table 1, which also reports NNH values).

NMA corroborated that unlicensed doses were associated with decreased tolerability in relation to licensed doses (16 studies; OR 2.02; 95% CI 1.19, 3.43; P = .01; moderate) (Figure 3B; eFigure 1,3; eTable 4).

*Acceptability*

 The dose-response curve for acceptability indicated similar findings to those for tolerability. NMA did not indicate significant differences in acceptability (20 studies; OR 1.59; 95% CI 0.93, 2.73; P = .09; low) between unlicensed and licensed doses (eResults 3).

*Heterogeneity, incoherence, and sensitivity analyses*

There was low (VPC $≅$ 0%) (change in ADHD symptoms; acceptability) and low-to-moderate (VPC < 50%) (tolerability) heterogeneity in the dose-response meta-analyses (eFigure 4,5; eResults 3).

There was low-moderate (tolerability: $τ$2 0.05; I2 8%) and moderate-high (change in ADHD symptoms: $τ$2 0.05; I2 68%; acceptability: $τ$2 0.24; I2 63%) heterogeneity in NMAs. There was no evidence of incoherence in any of the NMAs (eTable 5,6; eResults 3). Contour-enhanced funnel plots indicated some asymmetry for change in ADHD symptoms (eFigure 6-8; eResults 3).

The findings from the dose-response meta-analyses (eFigures 9-13; eResults 3) or the NMAs (Figure 3; eResults 3) did not change considerably in any of the sensitivity analyses. Notably, flexible-dose RCTs allowing titration beyond FDA recommendations were not associated with additional reductions of symptoms in relation to fixed-dose RCTs within FDA recommendations (SMD -0.34; 95% CI -0.82, 0.13; P = .16).

**Amphetamines**

*Change in ADHD symptoms*

The dose-response curve based on ten fixed-dose RCTs and 21 stimulant arms (dose range 12.5, 75 mg/d) demonstrated an initial sharp decrease followed by a plateau beyond 30-35 mg/d (Figure 4A; Table 1). Consistently, the ED50 was estimated at 12.5 mg/d while the ED95 was estimated at 30 mg/d.

NMA corroborated that unlicensed doses were not associated with larger reductions of symptoms in comparison to licensed doses (14 studies; SMD -0.08; 95% CI -0.24, 0.08; P = .31; very low) (Figure 3A; eFigure 14,15; eTable 4).

*Tolerability*

The dose-response curve based on seven fixed-dose RCTs and 15 stimulant arms (dose range 12.5, 75 mg/d) indicated a log-linear association with increments of 1.44% (95% CI 0.41%, 2.49%) on an exponential scale in the risk of dropping out due to adverse events for every 1 mg/d increase throughout the entire dose range for which data were available (Figure 4B; Table 1).

NMA did not indicate significant differences in tolerability (9 studies; OR 1.19; 95% CI 0.71, 2.02; P = .51; low) between unlicensed and licensed doses (Figure 3B; eFigure 14,16; eTable 4).

*Acceptability*

 The dose-response curve did not indicate a significant association with acceptability (P = .79). NMA corroborated there were no differences in acceptability (10 studies; OR 0.81; 95% CI 0.54, 1.22; P = .31; low) between unlicensed and licensed doses (eResults 3).

*Heterogeneity, incoherence, and sensitivity analyses*

There was low (tolerability), low-to-moderate (acceptability) and moderate-to-high (VPC ≥ 50%) (change in ADHD symptoms) heterogeneity in the dose-response meta-analyses (eFigure 17,18; eResults 3).

There was low heterogeneity in the NMAs (change in ADHD symptom severity: $τ$2 0.002; I2 55%; tolerability: $τ$2 < 0.0001; I2 0%; acceptability: $τ$2 0.04; I2 10%). There was some evidence of global incoherence (Q 5.09; P=.07) in the NMA for acceptability. There was no further evidence of incoherence in any of the NMAs (eTable 5,6; eResults 3). Contour-enhanced funnel plots did not indicate asymmetry for change in ADHD symptom severity (eFigure 19).

The findings from the dose-response meta-analyses (eFigures 20-26; eResults 3) or the NMAs (Figure 3; eResults 3) did not change considerably in any of the sensitivity analyses.

**DISCUSSION**

This study included data from 47 RCTs involving 7,714 participants to investigate treatment outcomes with licensed and unlicensed doses of stimulants in adults with ADHD. Based on averages, our findings indicated that higher doses of stimulants were generally associated with larger reductions of symptoms within the licensed range. For methylphenidate, unlicensed doses were associated with greater reductions of symptoms in relation to licensed doses; however, the incremental benefit was small and accompanied by considerable increase in the risk of treatment discontinuation due to adverse events. For amphetamines, unlicensed doses were not associated with additional reductions of symptoms in relation to licensed doses. There were especially few RCTs, particularly flexible-dose and low risk of bias studies, evaluating unlicensed doses for amphetamines, and it is possible that differences across stimulant classes at the unlicensed doses could be related to data availability. Therefore, our data could be interpreted as indicative that there are signals for greater improvement above the licensed range for stimulants in general, albeit those were clearer for methylphenidate than amphetamines based on the currently available RCTs*.* Regardless, taken together our findings indicated that, based on averages, unlicensed doses of stimulants may not have positive risk-benefits for adults with ADHD.

Further advances in precision medicine44 may enable the identification of individualized optimal doses and the stratification of patients by predicted positive/negative risk-benefits with unlicensed doses without the need for a trial-and-error process. Nevertheless, in the current absence of such personalized evidence base, intention-to-treat data from RCTs provide the best evidence currently available to guide decision making in routine clinical practice at the group-level (i.e., adults with ADHD). In fact, as our data reflect all the available information from similar patients who were treated with stimulants, they may be used by practitioners to inform clinical decision making around the choice of maximum doses.

Our findings indicate that adults with ADHD may experience the most reductions of symptoms with stimulants at licensed doses. While the tolerability of stimulants may continuously decrease with increments in dose, the additional reductions of symptoms with unlicensed doses may be small and possibly non-clinically meaningful (e.g., < 10-15 ADHD-RS reductions)45 in relation to the reductions of symptoms experienced with licensed doses. Therefore, in general practitioners should consider unlicensed doses cautiously.

Importantly, because the risk-benefits based on averages from our study will not generalize to every patient, our study does not provide evidence that practitioners should not trial unlicensed doses of stimulants in routine clinical practice. Indeed, individuals differ in their response to these medications46 and some adults with ADHD may experience larger reductions of symptoms, or less evident adverse events, with unlicensed doses than the average patient as reflected in our findings. Therefore, for a subgroup of patients, unlicensed doses may be well tolerated and required for the maximal reductions of symptoms and improvement in functioning. Stimulants are short-acting and their effects washout within the day, which enables the assessment of benefits and harms quickly, within 5-7 days.9,12 If needed (i.e., if harms outweigh the benefits), practitioners may go back to lower doses. It should also be considered that for some medications (e.g., mixed amphetamine salts), the licensed doses of extended-release formulations are smaller than those of immediate-release formulations, or of extended-release formulations in children, so that the unlicensed doses are not particularly high.

Overall, our study provides empirical support for expert-opinion that licensed doses may be sufficient for most patients10,11,47 while unlicensed doses may be considered eventually. Practitioners may trial unlicensed doses of stimulants in adults with ADHD who have shown partial response and good tolerability at the maximum licensed dose, but they should be aware that there may not be large gains in the patients’ response to the medication with those further increments in dose. Other strategies to augment response to stimulants (e.g., switching to other stimulant class) should be considered and may be implemented rather than simply raising the dose of stimulants.10 Our data calls into question the widespread use of unlicensed doses in routine practice as illustrated by data from the Swedish registry,48 despite earlier reports of relatively low doses in community treated adults from the US.49

Overall, the quality of evidence was not high, which underscores the importance of additional studies evaluating the impact of unlicensed doses of stimulants on the treatment outcomes of adults with ADHD. Flexible-dose RCTs may be particularly appropriate to study the risk-benefits of escalation to unlicensed doses because they ensure that participants receive optimal doses. Intriguingly, our sensitivity analyses focused on flexible-dose RCTs did not yield conclusive evidence of stronger associations between reductions of symptoms and unlicensed doses in comparison to associations from the main analyses. For methylphenidate, the point estimate was rather similar; for amphetamines, there was considerable imprecision, and the 95% CI was compatible with a relevant effect (SMD > 0.2) in both directions. While the scarcity of flexible-dose RCTs, particularly for amphetamines, may have limited the statistical power to detect differences, if those were large, they would likely be detected anyway.

Variation in how flexible-dose RCTs operationalized unlicensed doses may have contributed to the underestimation of the benefits of such high doses. For instance, for methylphenidate, for which most of the data were available, RCTs evaluating unlicensed doses, which were predominantly (80%) flexible-dose studies, were more likely to use weight-adjusted doses. While weight-adjusted doses have been shown to correlate poorly with reductions of symptoms in youth,50 and current practices are generally based on fixed dose schedules, current recommendations from CPGs about stimulant dosing in adults with ADHD have been based on data from RCTs that adopted weight-adjusted dosing14,15 and yielded the largest effect sizes across RCTs.16 Besides, RCTs evaluating unlicensed doses were also smaller and older than RCTs evaluating licensed doses; these characteristics may have contributed to larger effect sizes favoring unlicensed doses in relation to licensed doses.51 Regardless, our study highlights the need for additional rigorously conducted flexible-dose RCTs, which is in contrast with current FDA guidance on the development of stimulant drugs.

The most notable strengths of our study were our methodological rigor and the consistent results across different analytical strategies. However, our study also has limitations. First, although we made our best efforts to identify all available RCTs, we cannot rule out the possibility of having missed relevant studies. Second, extended-release medications have differing pharmacokinetic properties which could influence treatment outcomes even if given in the same total daily dose as immediate-release medications.52,53 However, we used dose equivalence because there were few RCTs for each medication. Future research should consider evaluating risk-benefit trade-offs for each medication separately if more data become available. Third, relatedly, our approach to compare doses of stimulants may not be directly translated into routine clinical practice because practitioners must also account for the differential impact of ADHD symptoms on activities along the day (e.g., morning organization, self-care; late-evening family interactions) when prescribing stimulants for adults with ADHD. Indeed, the COMACS study, albeit in children, showed that even two bioequivalent doses of different extended-release formulations of methylphenidate may have different effects on reductions of symptoms across the day depending on their immediate-/extended-release ratios.54 However, our analyses cannot account for these fine-grained variabilities across formulations, which would require specific experimental procedures (e.g., repeated assessments across the day, temporal sensitive rating scales) that are not typically adopted in the majority of RCTs. Fourth, for amphetamines we converted doses based on total amphetamine base equivalence because both d-/l-amphetamines are active; however, this does not account for differences in potency of d-/l-amphetamine as a dopamine/norepinephrine reuptake inhibitor,55 one of the proposed mechanisms of action for amphetamines.56 Nevertheless, other researchers in the field (e.g., investigators from the Multimodal Treatment Study of ADHD) have adopted similar approaches when assessing stimulant doses.57-59 Besides, our sensitivity analyses for the dose-response curves considering other conversion factors for stimulants did not yield considerable differences. Fifth, our definition of tolerability only considered dropouts due to any side effect. An examination of individual adverse events60 would be clinically informative, and future research should specifically examine this issue. Nevertheless, using dropout rates due to adverse events as a proxy for tolerability is a typical procedure in meta-analyses.13,23,51 Sixth, our analyses based on averages do not account for individual factors that could contribute to different dose-outcome associations (e.g., baseline symptoms,61 genetic background62). However, others have adopted similar procedures to investigate dose-response associations in psychiatry,63-65 general medicine66,67 and public health.68,69

**CONCLUSION**

The findings from this meta-analysis provide the best evidence currently available regarding treatment outcomes with licensed and unlicensed stimulants doses for adults with ADHD. Our results, based on averages, showed that most of the reductions of symptoms were associated with stimulants at licensed doses. Unlicensed doses were not only associated with small and possibly non-clinically meaningful additional reductions in symptoms, but also with marked decreased tolerability. Therefore, based on averages, unlicensed doses of stimulant may not have positive risk-benefits. In general, practitioners should consider unlicensed doses cautiously. Nevertheless, practitioners may trial unlicensed doses if needed and tolerated (e.g., for those who have shown partial response and good tolerability at the maximum licensed dose) because average observations will not generalize to every patient, and some may benefit from such high doses. However, practitioners should be aware that there may not be large gains in the patients’ response to the medication with those further increments in dose. Our findings should be incorporated in future recommendations from clinical practice guidelines to ensure transparent, evidence-based discussions with patients about expected risk-benefits (based on averages) with unlicensed doses of stimulants.

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*Concept and design:* Farhat, Polanczyk, Cipriani, Furukawa, Bloch, Cortese

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**FIGURE LEGENDS**

**Figure 1. Study selection**

The list of excluded records, with exclusion reasons, was provided in OSF (doi.org/10.17605/OSF.IO/47FS9)

**Figure 2. Dose-response curves for methylphenidate.**

Dose-response curve for change in ADHD symptom severity (A) and tolerability (B). The curves are presented until the maximum dose for which data were available for equivalent doses of methylphenidate. The shaded areas indicate 95% confidence intervals. The red dashed line indicates the FDA maximum recommended dose for immediate-release methylphenidate hydrochloride.

**Figure 3. Network estimates for stimulant doses beyond FDA recommendations against lower doses within FDA recommendations.**

Standardized mean difference (SMD) for change in ADHD symptoms (A) and odds ratio (OR) for tolerability (B) in network meta-analysis. All values are presented with 95% confidence intervals (95% CI). Blue, yellow and red square colors indicate moderate, low and very low certainty of evidence, respectively.

**Figure 4. Dose-response curves for amphetamine.**

Dose-response curve for change in ADHD symptom severity (A) and tolerability (B). The curves are presented until the maximum dose for which data were available for equivalent doses of amphetamines. The shaded areas indicate 95% confidence intervals. The red dashed line indicates the FDA maximum recommended dose for immediate release mixed amphetamine salts; the green dot dashed line indicates the FDA recommended maximum dose for lisdexamfetamine.

**TABLES**

**Table 1. Results per dose after conversion of SMD and OR to clinically interpretable values.**

|  |  |  |
| --- | --- | --- |
| **Dose (mg/d)** | **Change in ADHD symptom severity** | **Tolerability** |
| **Methylphenidate** | **Amphetamines** | **Methylphenidate** | **Amphetamines** |
| **SMD (95%CI)** | **ADHD-RS values, mean (95%CI)** | **SMD (95%CI)** | **ADHD-RS values, mean (95%CI)** | **OR (95%CI)**  | **RR (95%CI)**  | **NNH (95% CI**  | **OR (95%CI)**  | **RR (95%CI)**  | **NNH (95% CI**  |
| 0 | Ref | -9.7 | Ref | -9.7 | Ref | Ref | NA | Ref | Ref | NA |
| 5 | -0.06 (-0.08 to -0.04) | -9.76 (-9.99 to -9.53) | -0.14 (-0.18 to -0.10) | -10.68 (-11.14 to -10.22) | 1.12 (1.06 to 1.18) | 1.12 (1.06 to 1.18) | 412 (275 to 823) | 1.07 (1.02 to 1.13) | 1.07 (1.02 to 1.13) | 706 (380 to 2,468) |
| 10 | -0.13 (-0.17 to -0.09) | -10.57 (-11.03 to -10.11) | -0.27 (-0.36 to -0.19) | -12.18 (-13.21 to -11.26) | 1.25 (1.12 to 1.39) | 1.24 (1.12 to 1.38) | 198 (128 to 412) | 1.15 (1.04 to 1.28) | 1.15 (1.04 to 1.27) | 330 (177 to 1,234) |
| 15 | -0.19 (-0.25 to -0.13) | -11.26 (-11.95 to -10.57) | -0.39 (-0.52 to -0.27) | -13.55 (-15.05 to -12.18) | 1.39 (1.18 to 1.64) | 1.38 (1.18 to 1.62) | 128 (78 to 275) | 1.24 (1.06 to 1.45) | 1.23 (1.06 to 1.44) | 207 (111 to 823) |
| 20 | -0.25 (-0.32 to -0.17) | -11.95 (-12.75 to -11.03) | -0.49 (-0.64 to -0.34) | -14.70 (-16.43 to -12.98) | 1.55 (1.25 to 1.94) | 1.53 (1.24 to 1.90) | 91 (54 to 198) | 1.33 (1.08 to 1.64) | 1.32 (1.08 to 1.62) | 151 (78 to 618) |
| 25 | -0.30 (-0.39 to -0.21) | -12.52 (-13.55 to -11.48) | -0.56 (-0.73 to -0.39) | -15.51 (-17.46 to -13.55) | 1.74 (1.32 to 2.28) | 1.71 (1.31 to 2.22) | 68 (40 to 155) | 1.43 (1.11 to 1.85) | 1.42 (1.11 to 1.82) | 116 (59 to 449) |
| 30 | -0.35 (-0.45 to -0.25) | -13.09 (-14.25 to -11.95) | -0.61 (-0.79 to -0.42) | -16.09 (-18.16 to -13.90) | 1.94 (1.39 to 2.69) | 1.90 (1.38 to 2.60) | 54 (30 to 128) | 1.54 (1.13 to 2.09) | 1.52 (1.13 to 2.04) | 92 (46 to 380) |
| 35 | -0.40 (-0.51 to -0.29) | -13.67 (-14.94 to -12.41) | -0.63 (-0.81 to -0.44) | -16.32 (-18.39 to -14.13) | 2.16 (1.47 to 3.18) | 2.11 (1.46 to 3.04) | 44 (24 to 106) | 1.65 (1.15 to 2.37) | 1.63 (1.15 to 2.30) | 77 (37 to 330) |
| 40 | -0.44 (-0.55 to -0.33) | -14.13 (-15.39 to -12.87) | -0.63 (-0.82 to -0.44) | -16.32 (-18.50 to -14.13) | 2.42 (1.56 to 3.75) | 2.35 (1.54 to 3.55) | 36 (19 to 89) | 1.77 (1.18 to 2.68) | 1.74 (1.18 to 2.59) | 65 (30 to 275) |
| 45 | -0.47 (-0.59 to -0.36) | -14.47 (-15.86 to -13.21) | -0.63 (-0.82 to -0.43) | -16.32 (-18.50 to -14.02) | 2.7 (1.65 to 4.42) | 2.61 (1.63 to 4.13) | 30 (15 to 77) | 1.91 (1.20 to 3.03) | 1.87 (1.20 to 2.91) | 55 (25 to 248) |
| 50 | -0.50 (-0.61 to -0.39) | -14.82 (-16.09 to -13.55) | -0.62 (-0.82 to -0.42) | -16.20 (-18.50 to -13.90) | 3.01 (1.74 to 5.21) | 2.89 (1.71 to 4.79) | 26 (13 to 68) | 2.05 (1.23 to 3.42) | 2.01 (1.22 to 3.26) | 48 (21 to 216) |
| 55 | -0.53 (-0.63 to -0.42) | -15.17 (-16.32 to -13.90) | -0.62 (-0.83 to -0.40) | -16.20 (-18.62 to -13.67) | 3.36 (1.84 to 6.15) | 3.20 (1.81 to 5.56) | 22 (11 to 60) | 2.20 (1.25 to 3.87) | 2.15 (1.24 to 3.65) | 42 (18 to 198) |
| 60 | -0.55 (-0.65 to -0.44) | -15.39 (-16.55 to -14.13) | -0.61 (-0.83 to -0.39) | -16.09 (-18.62 to -13.55) | 3.76 (1.95 to 7.25) | 3.56 (1.91 to 6.42) | 19 (9 to 53) | 2.36 (1.28 to 4.38) | 2.30 (1.27 to 4.09) | 37 (16 to 177) |
| 65 | -0.57 (-0.67 to -0.46) | -15.62 (-16.77 to -14.36) | -0.60 (-0.84 to -0.37) | -15.97 (-18.73 to -13.32) | 4.20 (2.06 to 8.56) | 3.94 (2.02 to 7.40) | 16 (8 to 48) | 2.54 (1.30 to 4.95) | 2.46 (1.29 to 4.58) | 33 (14 to 165) |
| 70 | -0.58 (-0.69 to -0.47) | -15.74 (-17.00 to -14.47) | -0.60 (-0.85 to -0.34) | -15.97 (-18.84 to -12.98) | 4.68 (2.17 to 10.09) | 4.35 (2.12 to 8.49) | 14 (6 to 43) | 2.73 (1.33 to 5.6) | 2.64 (1.32 to 5.11) | 30 (12 to 151) |

**Table 1. Results per dose after conversion of SMD and OR to clinically interpretable values. (continued)**

|  |  |  |
| --- | --- | --- |
|  | **Change in ADHD symptom severity** | **Tolerability** |
|  | **Methylphenidate** | **Amphetamines** | **Methylphenidate** | **Amphetamines** |
| **Dose (mg/d)** | **SMD (95%CI)** | **ADHD-RS values, mean (95%CI)** | **SMD (95%CI)** | **ADHD-RS values, mean (95%CI)** | **OR (95%CI)**  | **RR (95%CI)**  | **NNH (95% CI**  | **OR (95%CI)**  | **RR (95%CI)**  | **NNH (95% CI**  |
| 75 | -0.60 (-0.72 to -0.48) | -15.97 (-17.35 to -14.59) | -0.59 (-0.86 to -0.32) | -15.86 (-18.96 to -12.75) | 5.23 (2.30 to 11.91) | 4.81 (2.24 to 9.72) | 13 (6 to 39) | 2.93 (1.36 to 6.33) | 2.82 (1.35 to 5.70) | 27 (10 to 138) |
| 80 | -0.62 (-0.75 to -0.48) | -16.20 (-17.70 to -14.59) | NA | NA | 5.84 (2.43 to 14.04) | 5.31 (2.36 to 11.06) | 11 (5 to 36) | NA | NA | NA |
| 85 | -0.63 (-0.78 to -0.49) | -16.32 (-18.04 to -14.70) | 6.52 (2.57 to 16.56) | 5.85 (2.49 to 12.53) | 10 (4 to 32) |

Doses in mg/d refer to immediate release methylphenidate hydrochloride and mixed amphetamine salts for methylphenidate and amphetamines, respectively.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; ADHD-RS = Attention-deficit/hyperactivity disorder rating scale; NA = Not applicable; NNH = Number needed to harm; OR = Odds ratio; RR = Relative risk; SMD = Standardized mean difference