Stimulant Medications and Sleep for Youth With ADHD: A Meta-analysis
Katherine M. Kidwell, MA, Tori R. Van Dyk, MA, Alyssa Lundahl, MA, Timothy D. Nelson, PhD

abstract

CONTEXT: Mixed findings exist on whether stimulant medications alter youth sleep.

OBJECTIVE: To determine the effect of stimulant medications on sleep.

DATA STUDIES: Studies published through March 2015 were collected via CINAHL, PsycINFO, and PubMed. References of retrieved articles were reviewed.

STUDY SELECTION: Eligibility criteria included studies with children/adolescents who had attention-deficit/hyperactivity disorder (ADHD), random assignment to stimulants, and objective sleep measurement. Studies that did not include information about key variables were excluded.

DATA EXTRACTION: Study-level, child-level, and sleep data were extracted by 2 independent coders. Effect sizes were calculated by using random effects models. Potential moderators were examined by using mixed effect models.

RESULTS: A total of 9 articles (N = 246) were included. For sleep latency, the adjusted effect size (0.54) was significant, indicating that stimulants produce longer sleep latencies. Frequency of dose per day was a significant moderator. For sleep efficiency, the adjusted effect size (−0.32) was significant. Significant moderators included length of time on medication, number of nights of sleep assessed, polysomnography/actigraphy, and gender. Specifically, the effect of medication was less evident when youth were taking medication longer. For total sleep time, the effect size (−0.59) was significant, such that stimulants led to shorter sleep duration.

LIMITATIONS: Limitations include few studies, limited methodologic variability, and lack of unpublished studies.

CONCLUSIONS: Stimulant medication led to longer sleep latency, worse sleep efficiency, and shorter sleep duration. Overall, youth had worse sleep on stimulant medications. It is recommended that pediatricians carefully monitor sleep problems and adjust treatment to promote optimal sleep.
Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurobehavioral disorder that occurs in ~7% of children and adolescents.\textsuperscript{1} Stimulant medication is the most common treatment of ADHD, with recent estimates indicating that ~3.5 million children in the United States are prescribed ADHD medications.\textsuperscript{2} Given the high occurrence of stimulant use, it is imperative to carefully examine potential adverse effects, including the influence stimulant medications may have on youth sleep.

Experts disagree about the effects of stimulant medications on the sleep of youth with ADHD. Some researchers have suggested that stimulants impair child sleep, citing evidence of objectively measured deficits in sleep quantity and quality, as well as parent reports of child insomnia, as common adverse effects of stimulant medications.\textsuperscript{3,4} Stimulants increase and maintain alertness, which could increase the time it takes to fall asleep (sleep latency) and reduce both total sleep time and sleep efficiency. These sleep-interfering effects may be particularly problematic when doses are taken later in the day (ie, closer to bedtime) or with extended-release versions that may remain active in the child’s body while preparing for bed.\textsuperscript{3}

Conversely, some researchers have argued that stimulants may actually improve a child’s sleep, noting that these medications are generally well tolerated and are effective in reducing the core symptoms of ADHD, and these positive effects may generalize to sleep problems as well.\textsuperscript{5,6} Sleep problems are common for youth with ADHD even when they are not taking medications,\textsuperscript{7} and some clinicians claim that children with ADHD sleep better when taking medications.\textsuperscript{8} Stein et al\textsuperscript{9} explained that difficulties falling asleep commonly observed in children with ADHD may be due to a “rebound effect” in which the child experiences withdrawal symptoms as the medication wears off near bedtime, suggesting that there may be benefits to maintaining active stimulants in the child’s body even in the hours approaching bedtime. Furthermore, stimulant medications may positively influence sleep indirectly by improving compliance and reducing bedtime resistance (a common problem for children with ADHD), thereby allowing children to fall asleep faster.\textsuperscript{8}

The effects of poor sleep on the emotional, cognitive, and physical functioning of youth are well documented,\textsuperscript{10–12} making the issue of how stimulants affect child sleep a critical one. Pediatricians need to know the potential effects of stimulant medications on sleep, either positive or negative. This information can then be considered along with potential effects on core ADHD symptoms to make informed decisions about prescribing these medications to children with ADHD. However, because the results of previous studies have been mixed,\textsuperscript{13–16} a simple review of the literature may not be sufficient to yield clear conclusions on this critical issue. This situation is ideal for a meta-analysis, which pools results across studies by using rigorous empirical methods to summarize the findings emerging from the literature. Furthermore, meta-analysis allows for examination of moderators, including methodologic variations that may explain some of the differences in findings across studies.

The purpose of the present study was to conduct a meta-analysis synthesizing the results from randomized controlled trials (RCTs) by using the objective measurement of sleep to determine the effects of stimulant medications on sleep in youth with ADHD. The effect sizes of objectively measured sleep outcomes were estimated, and key study-level, child-level, and procedural moderators were examined.

**METHODS**

**Study Selection**

From February 2014 to March 2015, two of the authors systematically collected research studies examining the effect of stimulant medications on the sleep of children with ADHD. Research articles were collected via CINAHL (EBSCO), PsycINFO, and PubMed. Search terms included the following: ADHD, ADD, stimulant, and sleep. These search terms were entered in various groups to facilitate a comprehensive search (ADHD + Stimulant + Sleep, ADD + Stimulant + Sleep, ADHD + Sleep, ADD + Sleep, Stimulant + Sleep, ADHD + Stimulant, and ADD + Stimulant). Discrepancies were resolved through discussion until consensus was reached.

References of relevant articles were also hand-searched for additional studies and the “Related Articles” and “Cited by” functions in search engines were used.

To focus on the most methodologically rigorous studies, eligibility criteria included studies that had child/adolescent participants diagnosed with ADHD, randomly assigned participants to stimulant medication conditions, and measured sleep by using actigraphy or polysomnography (PSG). Exclusion criteria included studies that did not provide enough statistical information to calculate effect sizes of key sleep variables. For a study that did not provide SDs of objectively measured sleep variables, the study author was contacted in an effort to obtain additional statistical information. No restrictions were placed on geographic location or publication year. If studies included >1 experimental condition in the within-subjects design, a decision was made as to what condition to include in the analyses (both conditions could not be included because this approach would introduce dependency in the data). Specifically, for the Santisteban et al\textsuperscript{17} study, the mixed amphetamine salts condition
was used to increase the power of the analyses examining differences between amphetamine and methylphenidates (due to the low number of studies that examined amphetamines). For the study by Corkum et al,\(^3\) the low-dose condition (as opposed to the moderate-dose condition) was used as a conservative estimate of the effect that stimulants have on sleep to avoid biasing the results. The guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses group were followed.\(^18\)

**Study Quality**

Medication trials can be conducted and controlled in varying ways. As such, examining the quality of such trials is appropriate. However, constructing a study quality variable from factors that are multidimensional and unrelated is minimally informative and potentially misleading.\(^19,20\) As such, researchers have recommended coding aspects of study quality that represent internal validity (eg, random assignment/counterbalancing), external validity (eg, recruitment procedures), and construct validity (eg, reliability of measure) and then analyzing the effect that these factors have on study outcomes. As such, in the present meta-analysis, the effects of such factors were analyzed separately in moderator analyses. Consistent with the Cochrane tool of bias, factors related to study quality included whether the study was peer reviewed, organization that produced the report (ie, university, government entity, contract research firm, hospital), recruitment source (ie, random, school, hospital clinic, combination, part of larger study), inclusion and exclusion criteria, use of random assignment, type of sample recruited (ie, nationally representative versus convenience), method by which ADHD was diagnosed (ie, clinical interview only; rating scale only; combination of interviews, observation, and assessment), inclusion of comorbidities, previous mental health treatment, whether compensation was given, blinding of conditions, the method used to assess sleep (ie, PSG or actigraphy), and funding source (ie, whether funded by a pharmaceutical company). However, because there was little to no variation between studies on whether the report was peer reviewed, the organization that produced the report, recruitment source, inclusion and exclusion criteria, whether random assignment was used, type of sample recruited, how ADHD was diagnosed, inclusion of comorbidities, previous mental health treatment, compensation of participants, or the blinding of conditions, these variables were not examined in analyses.

**Data Extraction**

In addition to coding for factors related to study quality, a number of potential moderators were coded as outlined in Table 1. One of the categorical variables in Table 1 (ie, whether the medication was short-, medium-, or long-acting) did not have enough variability across conditions to be included in analyses as a moderator but is presented in the table for descriptive purposes. Two independent coders coded the studies, and the inter-rater reliability on outcomes and moderators was excellent (mean \(\kappa = 0.88\); range: 0.59–1.00).\(^21\) Any inconsistencies were resolved through discussion until the coders reached consensus.

**Effect Size Calculation**

Calculating effect sizes in a meta-analysis provides a common metric for combining results across diverse studies while delivering a standardized estimate of both the direction and magnitude of the intervention effect.\(^22\) The present meta-analysis calculated 3 sets of effect sizes based on 3 different comparisons: (1) sleep latency of baseline sleep versus medicated sleep; (2) sleep efficiency of baseline sleep versus medicated sleep; and (3) total sleep time of baseline versus medicated sleep. Although a variety of sleep outcomes were coded for in the analysis (eg, wake after sleep onset; percent awake; percentage of time in stages 1, 2, 3, and rapid-eye movement), only sleep efficiency, sleep latency, and total sleep time were supported by a sufficient number of studies to calculate reliable effect sizes. When baseline sleep outcomes were not reported for the study, the sleep outcomes for the placebo group were imputed (\(k = 4\) studies).

All studies included in this meta-analysis used a within-subjects or repeated measures design. Rather than focusing on change between people, repeated measures studies focus on change within a person. The formula to calculate the effect size for a repeated measures study uses the SD of change scores, rather than the SD of raw scores.\(^23\) The SD of change scores, however, is rarely reported by original studies. However, if one assumes equal SDs in the preintervention and postintervention populations, it is possible to estimate the repeated measures effect size from a between-subjects effect size by using a conversion equation. The between-subjects effect size can then be converted to a within-groups effect size by taking into account the correlation \(r\) between the preintervention and postintervention scores. Again, however, original studies rarely report the correlation between preintervention and postintervention scores. When sufficient information was not obtained, a between-subjects effect size was calculated as the best estimate (ie, \(r\) was estimated to be 0.5). This approach has been used in previous published meta-analyses of sleep outcomes in both adults and children.\(^24,25\) This assumption results in a downward bias (toward zero) of effect size estimates (thus, conservative estimates) and unintended heterogeneity due to an
TABLE 1 Coded Characteristics for Each Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (ES)</th>
<th>w</th>
<th>N</th>
<th>Length of Time on Medication, d</th>
<th>Release Type</th>
<th>Mean Total Dosage/d, mg</th>
<th>Frequency Dosage/d</th>
<th>Frequency Stimulants/ wk</th>
<th>No. of Nights Assessed</th>
<th>Method of Sleep Assessment</th>
<th>Stimulant Medication Class</th>
<th>Pharmaceutical Company Funding</th>
<th>Proportion of Male Subjects in Sample, %</th>
<th>Mean Age of Sample, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep latency: baseline sleep versus medicated sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chattoor et al</td>
<td>-1.76</td>
<td>2.53</td>
<td>7</td>
<td>2.5</td>
<td>LA</td>
<td>30.0</td>
<td>3.0</td>
<td>2.5</td>
<td>1</td>
<td>PSG</td>
<td>AMP</td>
<td>Yes</td>
<td>108.0</td>
<td></td>
</tr>
<tr>
<td>Corkum et al</td>
<td>-0.07</td>
<td>55.16</td>
<td>21</td>
<td>7.0</td>
<td>SA</td>
<td>22.5</td>
<td>3.0</td>
<td>7.0</td>
<td>28</td>
<td>Actigraphy</td>
<td>MPH</td>
<td>No</td>
<td>71.0</td>
<td>102.0</td>
</tr>
<tr>
<td>Galland et al</td>
<td>-0.878</td>
<td>36.83</td>
<td>27</td>
<td>2.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Giblin and Strobel</td>
<td>0.48</td>
<td>21.58</td>
<td>16</td>
<td>28.0</td>
<td>LA</td>
<td>48.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PSG</td>
<td>AMP</td>
<td>Yes</td>
<td>41.7</td>
<td>126.0</td>
</tr>
<tr>
<td>Santisteban et al</td>
<td>-0.16</td>
<td>90.58</td>
<td>34</td>
<td>5.0</td>
<td>SA</td>
<td>—</td>
<td>2.0</td>
<td>7.0</td>
<td>14</td>
<td>Actigraphy</td>
<td>MPH</td>
<td>No</td>
<td>7.72</td>
<td>116.0</td>
</tr>
<tr>
<td>Schwartz et al</td>
<td>0.48</td>
<td>92.60</td>
<td>44</td>
<td>7.0</td>
<td>SA</td>
<td>—</td>
<td>2.0</td>
<td>7.0</td>
<td>28</td>
<td>Actigraphy</td>
<td>MPH</td>
<td>No</td>
<td>84.1</td>
<td>110.4</td>
</tr>
<tr>
<td>Tirosh et al</td>
<td>0.79</td>
<td>11.86</td>
<td>10</td>
<td>8.0</td>
<td>MA</td>
<td>15.6</td>
<td>1.25</td>
<td>7.0</td>
<td>12</td>
<td>Actigraphy</td>
<td>MPH</td>
<td>No</td>
<td>72.7</td>
<td>116.0</td>
</tr>
<tr>
<td><strong>Sleep efficiency: baseline sleep versus medicated sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
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<td>7</td>
<td>2.5</td>
<td>LA</td>
<td>30.0</td>
<td>3.0</td>
<td>2.5</td>
<td>1</td>
<td>PSG</td>
<td>AMP</td>
<td>Yes</td>
<td>108.0</td>
<td></td>
</tr>
<tr>
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<td>21</td>
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<td>7.0</td>
<td>28</td>
<td>Actigraphy</td>
<td>MPH</td>
<td>No</td>
<td>71.0</td>
<td>102.0</td>
</tr>
<tr>
<td>Galland et al</td>
<td>-0.878</td>
<td>36.83</td>
<td>27</td>
<td>2.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sanjil et al</td>
<td>0.48</td>
<td>25.45</td>
<td>12</td>
<td>28.0</td>
<td>LA</td>
<td>48.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PSG</td>
<td>AMP</td>
<td>Yes</td>
<td>41.7</td>
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<td>Tirosh et al</td>
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<td>12</td>
<td>Actigraphy</td>
<td>MPH</td>
<td>No</td>
<td>72.7</td>
<td>116.0</td>
</tr>
</tbody>
</table>

Negatives effect size represents lower sleep efficiency and total sleep time values after being medicated with a stimulant; positive effect size represents greater sleep latency values after being medicated with a stimulant. The length of time on medication (days) was coded as number of days in the study that the child took stimulant medications. The length of time on medication (days) was coded as number of days in the study that the child took stimulant medications. The release type was how long the stimulants are expected to last (short-acting [SA], medium-acting [MA], or long-acting [LA]). The mean total dosage per day (in milligrams) was coded as the average milligrams of stimulants that children took in a day. The frequency dosage per day was coded as the number of times a child took stimulants in a day. The frequency stimulants per week were coded as number of days a week the child took medication. The number of nights assessed were coded as the number of nights a child wore an actigraphy or participated in overnight PSG. Method of sleep assessment was coded as 1 = actigraphy, 2 = PSG. Stimulant medication class was coded as 1 = methylphenidate (MPH), 2 = amphetamine (AMP). Pharmaceutical company funding was coded as 0 = no, 1 = yes. Proportion of male subjects in the sample was coded as the number of male subjects divided by the number in total sample. The mean age of the sample was coded as mean age in months. ES = Hedges' g; N, number of youth in the study; w, inverse of the variance. —, indicates that the information was not available for that study.
After calculating the within-subjects effect size in the aforementioned manner, the effect sizes were adjusted for small sample size inflation by applying Hedges’ correction factor.\textsuperscript{26} The resulting effect size (Hedges’ g) assumes that each study’s variance is an estimate (rather than a constant). Mathematical signs were adjusted so that a negative effect size represented poorer sleep performance after medication. Within-studies variance due to sampling error was calculated according to standard guidelines.\textsuperscript{23}

**Meta-analytic Procedure**
Meta-analysis macros for SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY)\textsuperscript{22} were used to conduct the main effect and moderator analyses. Given the expected heterogeneity of the studies based on varying study designs, random effects models (with maximum likelihood) were used to estimate the pooled effect sizes. Mixed effect models (both fixed and random effects) were used to examine moderators. For continuous and dummy-coded binary moderators, weighted least squares regressions were used with random effects variance components calculated by using residuals. The SE of the regression coefficient was divided by the square root of the mean-square residual, and this adjusted value was then used in a z test to ensure an accurate test of significance for the meta-analytic computations.

Heterogeneity of the effect sizes (as indicated by the \(Q\) statistic and the \(I^2\) statistic) was tested. The \(Q\) statistic is calculated as the weight sum of squared differences between the individual study effects and the pooled effect across all included studies. \(I^2\) represents the percentage of variation across studies due to heterogeneity.

To determine the effect of publication bias on the overall effect size, “trim and fill” analyses were conducted.\textsuperscript{27,28} These analyses involve plotting the effect size of each study against its precision (1/SE). If no publication bias exists, the plot is shaped like a funnel. However, studies with nonsignificant results or studies with small sample sizes are often not published. This approach results in a bias such that studies in the bottom left-hand corner of the plot (for positive effect sizes) or the bottom right-hand corner of the plot (for negative effect sizes) tend to be missing.\textsuperscript{27} Using the effect sizes, the studies plotted farthest to the left of the graph (considered symmetrically unmatched) were trimmed. The missing counterparts (mirror images of the trimmed studies) were imputed, allowing for computation of adjusted effect sizes and confidence intervals (CIs).

**RESULTS**
From the 9927 nonduplicate articles identified and screened in the literature search, 167 full texts were examined (Fig 1). A total of 158 articles were excluded (see Supplemental Information), leaving 9 articles in the final sample. Demographic characteristics for each of the study samples are reported in Table 1.

The Effect of Stimulant Medications on Sleep Latency of Children With ADHD
A total of 7 samples (\(N = 171\)) examined the effect of stimulant medication on the sleep latency of children with ADHD diagnosed on the basis of formal criteria. The overall effect size of 0.78 was significant, indicating that stimulant medication was associated with a longer sleep latency (95% CI: 0.54 to 1.02; \(Q[6] = 18.35\); \(P = .054\); \(I^2 = 67.30\%\)) (Fig 2). The \(I^2\) index of 67.30% indicates a moderate to high amount of heterogeneity in effect sizes across studies.\textsuperscript{19} The trim and fill method for addressing publication bias\textsuperscript{27,28} revealed asymmetry in the funnel plot for the difference in sleep latency outcomes between baseline sleep and medicated sleep. Three studies to the right of the mean were unmatched. These 3 studies were imputed to the left of the mean, resulting in a significant and moderate adjusted effect size of 0.54 (95% CI: 0.28 to 0.81; \(Q[6] = 58.30\); \(P < .001\)) (plots not shown).

A significant moderator of the sleep latency effect was the frequency of dosage per day. For every additional time the medication was taken per
day, the effect size became greater (ie, more positive) by 0.42 (Table 2). Thus, the effect of stimulant medication on sleep latency became greater when the stimulant was taken more frequently throughout the day, such that more frequent doses were associated with longer sleep latency. No other variables emerged as significant moderators of the effect of stimulant medication on sleep latency.

### The Effect of Stimulant Medications on Sleep Efficiency of Children With ADHD

A total of 7 samples ($N = 155$) examined the effect of stimulant medications on the sleep efficiency of children with ADHD. The overall effect size of $-0.39$ was significant, indicating that stimulant medication was associated with poorer sleep efficiency (95% CI: $-0.69$ to $-0.08$; $Q[6] = 36.08; P < .001$; $I^2 = 83.37\%$) (Fig 3). The $I^2$ index of 83.37% indicates a high amount of heterogeneity in effect sizes across studies.$^{19}$ The trim and fill method for addressing publication bias$^{27,28}$ revealed asymmetry in the funnel plots for the difference in sleep efficiency outcomes between baseline sleep and medicated sleep. One study was on the right of the mean, resulting in a significant and small-to-moderate adjusted effect size of $-0.32$ (95% CI: $-0.63$ to $-0.01$; $Q[6] = 41.75; P < .001$) (plots not shown).

Significant moderators included both methodologic/design factors (eg, length of time on medication, the number of nights that sleep was assessed, the method by which sleep efficiency was assessed), and sample characteristics (eg, the percentage of male subjects in the sample) (Table 3). With regard to length of time on medication, for every 1-day increase in the length of time youth were on medication, the effect size (ie, the difference in sleep efficiency between baseline sleep efficiency and medicated sleep efficiency) became less negative by 0.05. Thus, the negative effect of stimulant medication on youth’s sleep efficiency is lessened when he or she is on medication for longer periods. In terms of the number of nights that sleep was assessed, for every additional night, the effect size became less negative by 0.04. Thus, the negative effect of stimulant medication on youth’s sleep efficiency becomes less as more nights were assessed. Lastly, when PSG was used to assess sleep efficiency (compared with actigraphy), the effect size was more negative by 0.81. Thus, the negative effect of stimulant medication on youth’s sleep efficiency is more apparent when assessed via PSG than via actigraphy. In regard to gender, for every 1-percentage increase in the proportion of male subjects in the sample, the effect size became more negative (stronger) by 0.02. Thus, the negative effect of stimulant medication on youth’s sleep efficiency was greater for boys than for girls.

### The Effect of Stimulant Medications on Total Sleep Time of Children With ADHD

A total of 7 samples ($N = 223$) examined the effect of stimulant medication on the total sleep time of

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**TABLE 2 Summary of Moderator Analyses for Sleep Latency**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$k$</th>
<th>$b$</th>
<th>$Q$ Regression</th>
<th>$Q$ Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodologic/design characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of time on medication (in days)</td>
<td>7</td>
<td>0.005</td>
<td>$(1) = 0.76$, $P = .38$</td>
<td>$(15) = 6.43$, $P = .27$</td>
</tr>
<tr>
<td>Mean total dosage/d (in milligrams)</td>
<td>4</td>
<td>$-0.01$</td>
<td>$(1) = 3.82$, $P = .051$</td>
<td>$(12) = 1.75$, $P = .42$</td>
</tr>
<tr>
<td>Frequency of dosage/d</td>
<td>5</td>
<td>0.42**</td>
<td>$(1) = 10.24$, $P = .001$</td>
<td>$(15) = 5.56$, $P = .15$</td>
</tr>
<tr>
<td>Frequency of dosage/wk</td>
<td>5</td>
<td>0.02</td>
<td>$(1) = 0.04$, $P = .85$</td>
<td>$(13) = 3.77$, $P = .29$</td>
</tr>
<tr>
<td>No. of nights of sleep assessed</td>
<td>7</td>
<td>0.01</td>
<td>$(1) = 2.01$, $P = .16$</td>
<td>$(15) = 5.72$, $P = .34$</td>
</tr>
<tr>
<td>Method of sleep latency assessment</td>
<td>7</td>
<td>$-0.17$</td>
<td>$(1) = 0.62$, $P = .043$</td>
<td>$(13) = 5.52$, $P = .36$</td>
</tr>
<tr>
<td>Stimulant medication class</td>
<td>7</td>
<td>$-0.29$</td>
<td>$(1) = 1.29$, $P = .25$</td>
<td>$(15) = 5.44$, $P = .38$</td>
</tr>
<tr>
<td>Funding source</td>
<td>7</td>
<td>0.04</td>
<td>$(1) = 0.03$, $P = .86$</td>
<td>$(15) = 6.08$, $P = .30$</td>
</tr>
<tr>
<td>Sample characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>6</td>
<td>0.005</td>
<td>$(1) = 0.56$, $P = .55$</td>
<td>$(14) = 5.26$, $P = .26$</td>
</tr>
<tr>
<td>Age</td>
<td>7</td>
<td>$-0.007$</td>
<td>$(1) = 0.26$, $P = .61$</td>
<td>$(15) = 5.59$, $P = .35$</td>
</tr>
</tbody>
</table>

$d$: unstandardized regression coefficient; $k$: number of studies; $Q$: Regression, homogeneity test for regression (ie, regression sum of squares); $Q$: Residual, sum-of-squares residual (represents sampling error and random variation).

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children with ADHD. The overall effect size of −0.59 was moderate and significant, indicating that stimulant medication was associated with shorter total sleep time (95% CI: −0.84 to −0.35); Q(6) = 34.62; P < .001; \( \hat{I}^2 = 82.67\% \) (Fig 4). The \( \hat{I}^2 \) index of 82.67% indicates a high amount of heterogeneity in effect sizes across studies.\(^19\) The trim and fill method for addressing publication bias\(^{27,28}\) revealed no asymmetry in the funnel plots for the difference in total sleep time outcomes between baseline sleep and medicated sleep, indicating no publication bias. No significant moderators emerged (Table 4).

### DISCUSSION

In RCTs using objective measurements of sleep, stimulant medications led to longer sleep latency, worse sleep efficiency, and shorter sleep duration. Overall, children and adolescents had worse sleep when they took stimulant medications. For sleep latency, frequency of dose moderated the relationship between stimulants and sleep. The more times a day a stimulant was taken, the longer it took for the child to fall asleep. Thus, these results suggest that the recommendation of taking a third dose after school to prevent the rebound effect\(^8\) may not be helpful.

The more frequently a medication is taken throughout the day, the more likely it is to be in the child’s system when he or she tries to fall asleep, thus impairing sleep latency.

Frequency of daily dosage also reflects the type of medication (extended release versus immediate release), such that children often take immediate-release formulas 2 to 3 times a day and extended-release formulas only once a day. Extended-release formulas wear off in 8 to 12 hours and seem to have less of an effect on sleep latency than immediate-release formulas that are taken 3 times a day with a dose close to bedtime.

For sleep efficiency, there were several methodologic and sample characteristic moderators. Stimulants had a negative effect on sleep regardless of how long children took medication. However, as youth took stimulants for longer durations, sleep efficiency became “less bad”; that is, children seemed to adjust to the medication the more days they took stimulants during the study. This finding is mostly consistent with a frequently proposed, but rarely tested, argument that youth adjust to medication over time and may have initial sleep problems that will resolve.\(^9,29\) Although sleep problems did not resolve entirely, sleep efficiency was not as poor when children stayed on medications longer. Similarly, the more nights that sleep was assessed during the study, the less negative effects on sleep efficiency were observed. In addition, although only 2 PSG studies were included in this analysis, PSG was more sensitive to sleep efficiency differences than actigraphy, which is consistent with the view that PSG is the gold standard for objective sleep assessment.\(^30\) Finally, boys’ sleep efficiency was worse than girls’ when taking stimulant medications.

For sleep duration, there were no significant moderators.

### TABLE 3 Summary of Moderator Analyses for Sleep Efficiency

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>k</th>
<th>b</th>
<th>Q Regression</th>
<th>Q Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodological/design characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of time on medication, d</td>
<td>7</td>
<td>0.05**</td>
<td>Q(1) = 17.00, ( P &lt; .001 )</td>
<td>Q(5) = 8.59, ( P = .13 )</td>
</tr>
<tr>
<td>Mean total dosage/d (in milligrams)</td>
<td>4</td>
<td>0.02**</td>
<td>Q(1) = 7.91, ( P = .005 )</td>
<td>Q(2) = 8.89, ( P = .01 )</td>
</tr>
<tr>
<td>Frequency of dosage/d</td>
<td>5</td>
<td>0.25</td>
<td>Q(1) = 3.63, ( P = .06 )</td>
<td>Q(3) = 7.33, ( P = .06 )</td>
</tr>
<tr>
<td>Frequency of dosage/wk</td>
<td>5</td>
<td>0.13</td>
<td>Q(1) = 2.25, ( P = .13 )</td>
<td>Q(3) = 5.59, ( P = .13 )</td>
</tr>
<tr>
<td>No. of nights of sleep assessed</td>
<td>7</td>
<td>0.04*</td>
<td>Q(1) = 6.24, ( P = .01 )</td>
<td>Q(5) = 8.63, ( P = .13 )</td>
</tr>
<tr>
<td>Method of sleep efficiency assessment</td>
<td>7</td>
<td>−0.81**</td>
<td>Q(1) = 6.85, ( P = .008 )</td>
<td>Q(5) = 7.81, ( P = .16 )</td>
</tr>
<tr>
<td>Stimulant medication class</td>
<td>7</td>
<td>0.46</td>
<td>Q(1) = 1.72, ( P = .19 )</td>
<td>Q(5) = 11.44, ( P = .04 )</td>
</tr>
<tr>
<td>Funding source</td>
<td>7</td>
<td>0.45</td>
<td>Q(1) = 1.72, ( P = .19 )</td>
<td>Q(5) = 11.44, ( P = .04 )</td>
</tr>
<tr>
<td>Sample characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>6</td>
<td>−0.02**</td>
<td>Q(1) = 10.40, ( P = .001 )</td>
<td>Q(4) = 6.08, ( P = .19 )</td>
</tr>
<tr>
<td>Age</td>
<td>7</td>
<td>0.006</td>
<td>Q(1) = 0.079, ( P = .77 )</td>
<td>Q(5) = 8.62, ( P = .13 )</td>
</tr>
</tbody>
</table>

\(^a\) unstandardized regression coefficient; \( k \), number of studies; \( Q \) Regression, homogeneity test for regression (ie, regression sum of squares); \( \hat{Q} \) Residual, sum-of-squares residual (represents sampling error and random variation).

\(^*\) \( P < .01 \); \(^*\) \( P < .05 \); \(^**\) \( P < .001 \); \(^*\) \( P < .05 \).
Clinical and Research Implications

The results of the present meta-analysis highlight the importance of carefully weighing the potential benefits and adverse effects of stimulant medications when prescribing to children. Sleep impairment is related to many cognitive (eg, inattention) and emotional/behavioral (eg, defiance, anger) consequences, and sleep adverse effects could undermine the benefits of stimulant medications in some cases. Pediatricians are advised to frequently monitor the effects of stimulant medications, including potential adverse effects such as sleep disturbance. A wide range of medication options are currently available for treating ADHD, and pediatricians should carefully consider the medication dosage, release type (eg, immediate release versus extended release), and frequency to minimize potential sleep problems while effectively treating ADHD symptoms. Pediatricians are also encouraged to provide referrals for behavioral treatment of ADHD and sleep, either in addition to or as an alternative to prescribed medications. In terms of research, the limited number of published RCTs that include measurement of sleep highlights the need for more studies reporting additional sleep variables (eg, rapid-eye movement sleep latency). Such studies would help to move our knowledge of the effects of stimulants on youth sleep beyond basic indicators of sleep (latency, efficiency, and duration), and provide a more sophisticated and nuanced understanding of the precise ways in which medications and sleep interact.

Limitations

Although there are many strengths of the present study, several limitations must be noted. Unpublished studies may have resulted in biased findings, and publication bias did exist for sleep latency and sleep efficiency effect sizes. Thus, these results should be interpreted with that limitation in mind, as the effect sizes may not be representative of all studies examining the effects of stimulants on the sleep of children with ADHD. Specifically, the correction applied to the results may underestimate the effect of stimulants on sleep. Similarly, relationships between moderators and effect sizes may not be truly representative of actual relationships between the constructs, especially given the small number of studies and limited variability between studies. This limitation is an especially important consideration to remember when interpreting null findings. In addition, the impact of some moderators could not be examined due to the lack of variability between studies. Finally, multiple regression analyses could not be completed due to inconsistent reporting of similar variables across studies; therefore, it is unclear what the unique contribution of each moderator is.

There are also limitations to the existing studies that examine the effect of stimulant medications on sleep. Nearly every study used a within-subjects design. Meta-analyses of between-subjects designs would allow for improved comparison of dosing conditions (eg, 5 mg vs 25 mg) because within-subjects designs have dependency in the data that prevents comparisons using the same sample.
Moreover, many studies included children taking various doses of medication, which reduced the ability to compare dosing effects. In addition, no studies reported the necessary statistics (eg, test–retest reliability of measures and SD of change scores) needed to calculate the true effect sizes in the articles. Reporting of reliability and SDs of change scores should become standard practice to facilitate future meta-analyses. These statistics may have not been reported because sleep is frequently measured as a secondary variable. Research that purposefully and carefully assesses sleep as a potential adverse effect has great implications for youth with ADHD. Finally, relatively few studies used objective measurements of sleep and random assignment, although these more rigorous methods provide for better estimates of the effect of medications on sleep. Given the relatively small number of studies available for inclusion in the present analysis, it will be important for the field to consider the results of any new high-quality studies that are published. As the relevant literature grows, additional meta-analyses may be warranted to update the conclusions that can be drawn from the extant literature.

**Strengths**

The present study has multiple strengths. First, the analyses included only RCTs to increase confidence in the findings. Second, this meta-analysis included only studies that specifically looked at sleep outcomes. Sleep outcomes were required to be measured objectively, as parent-report and child-report of sleep are often biased.³¹ Actigraphy and PSG allow for more accurate measurement of sleep latency, sleep efficiency, and total sleep time. Third, this study used rigorous random effect and mixed effect meta-analytic techniques to explore moderators that have not yet been examined. Moderators allow clinicians to have a more nuanced understanding of the effects of medication on sleep and provide researchers with guidance on how to design effective studies. Fourth, publication bias analyses were conducted to provide the truest estimates of effect size.

**CONCLUSIONS**

Stimulant medications impair the sleep of children and adolescents, as evidenced by findings using rigorous methods. It is recommended that pediatricians carefully assess for sleep problems in children with ADHD and monitor medication type and dosage schedules to promote optimal sleep and minimize medication-induced sleep impairments.

**ABBREVIATIONS**

ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
PSG: polysomnography
RCT: randomized controlled trial

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