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Effect of Extended-Release Dexamethylphenidate and Mixed Amphetamine Salts on Sleep: A Double-Blind, Randomized, Crossover Study in Youth with Attention-Deficit Hyperactivity Disorder

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Abstract

Objective—We sought to determine the dose-response effects of extended-release (ER) dexamethylphenidate (d-MPH) and ER mixed amphetamine salts (MAS) on objective measures of sleep.

Methods—This was an 8-week, double-blind, placebo-controlled, randomized, two period, crossover study of youth with attention-deficit hyperactivity disorder (ADHD) as confirmed by the Kiddie Schedule for Affective Disorders for School-Age Children—Present and Lifetime version (K-SADS-PL). Children aged 10–17 years were recruited from clinical practice, colleague

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referrals, and flyers. Participants were randomized to initially receive either d-MPH or MAS. During each 4-week drug period, children received three dose levels (10, 20, and 25/30 mg) in ascending order, with placebo substituted for active medication in a randomized fashion during 1 week of the study. After 4 weeks, participants were switched to the alternative medication for another 4 weeks of treatment. The main outcome measure was sleep duration as measured by actigraphy. Children, parents, and researchers were blinded to drug, dose, and placebo status.

Results—Sixty-five participants met the inclusion criteria and were enrolled in the study. Of these, 37 participants with sufficient sleep data for analysis were included. Sleep schedule measures showed a significant effect for dose on sleep start time ($F_{(1,36)} = 6.284$; $p < 0.05$), with a significantly later sleep start time when children were receiving 20- or 30-mg doses, compared with placebo ($p < 0.05$). A significant dose effect was found on actual sleep duration ($F_{(1,36)} = 8.112$; $p < 0.05$), with significantly shorter actual sleep duration for subjects receiving 30 mg compared with those receiving placebo ($p < 0.05$). There were no significant differences on sleep duration or sleep schedule between the two stimulant medications. The trial is complete and closed to follow-up.

Conclusions—Higher stimulant doses were associated with reduced sleep duration and later sleep start times, regardless of medication class.

Trial registration—ClinicalTrials.gov: NCT00393042.

1 Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterized by impulsivity, hyperactivity, and inattention [1], and affects a reported 5.29 % of children and adolescents worldwide [2]. The first-line treatment for ADHD is stimulant medication, which includes immediate-release (IR) and delayed-release formulations of methylphenidate (MPH) and amphetamine. Stimulants affect the levels of dopamine (DA) and norepinephrine (NE) by altering the function of the DA transporter (DAT) and NE transporter (NET), inhibiting reuptake of the chemicals at nerve endings and increasing their levels and activity on the post-synaptic neuron [3]. Presumably, increasing catecholamine levels in the frontal cortex and the striatum results in symptomatic improvement in ADHD [4]. Both MPH and amphetamines inhibit the reuptake of NE and DA; however, amphetamines are also associated with the release of catecholamines into the synapses [3].

MPH is the most frequently prescribed stimulant medication for ADHD worldwide [5, 6]. It is a racemic mixture of dextro- and levo-isomers of MPH. Dexmethylphenidate (d-MPH) contains only the dextro-isomer. Amphetamine is available as mixed amphetamine salts (MAS), a racemic mixture, as well as dexamphetamine (the dextro-isomer) and lisdexamfetamine (a prodrug). Extended-release (ER) stimulant formulations have largely replaced IR formulations as first-line treatments for ADHD due to their longer duration of behavioral effects and increased convenience. The use of IR medication not only increases the likelihood of missed doses, but can also be problematic for children as they are required to take a second dose at school and a third dose is needed to provide coverage during homework and after-school activities. The duration of the behavioral effect of IR formulations is approximately 4 h. ER MAS and d-MPH provide half of the medication as

an IR, with a second pulse 4–6 h later. ER formulations of d-MPH have a duration of effect on behavior of 8–12 h [7]. The literature suggests that individuals with ADHD are satisfied with ER formulations and have increased compliance compared with IR [8].

Stimulants' increase of synaptic DA and NE enhance the wake-promoting pathways in the ascending arousal system while also inhibiting sleep-promoting neurons in the ventrolateral preoptic area [9]. Insomnia is one of the most common acute stimulant side effects of both IR and ER stimulant formulations, with 17–32 % of children developing severe insomnia [10, 11]. Furthermore, over time sleep deprivation can cause or exacerbate ADHD symptoms, such as inattention or behavioral dysregulation [3]. In children with ADHD, only 1 h less sleep a night can cause clinically significant deterioration of neurobehavioral scores [12]. Therefore, children who are affected by sleep side effects such as insomnia may have worse clinical outcomes if insomnia secondary to stimulant medication exacerbates ADHD or associated neurobehavioral problems.

The most frequent reasons for discontinuing treatment are lack of efficacy and not being able to tolerate the side effects [13]. Poor tolerability of the stimulant may lead to lower doses being prescribed, and thus may limit the efficacy of the treatment. Community healthcare providers tend to utilize lower stimulant doses, perhaps resulting in better tolerated, albeit less effective, treatment [14, 15]. The goal of titration is to determine the most effective dose that is well tolerated [16]. While lower doses are generally less effective, higher doses are more likely to increase insomnia and decrease appetite [11]. Dose-response studies can help practitioners understand the impact of the medication dose on adverse events as well as symptomatic improvement.

However, there are few comparative effectiveness studies of frequently utilized MPH and amphetamine medications for ADHD that have evaluated sleep and adverse events, and it remains unclear if there are differential effects of drug and/or dose on sleep. In the absence of these data, choice of stimulant and dose is often based upon a trial and error basis. Increased knowledge of the effects of stimulant class and dose on sleep can help guide clinicians and patients in choosing a medication and providing information regarding potential side effect risks.

In the present study, we sought to determine if there are significant differences in the dose-response effects of ER d-MPH and ER MAS on objective measures of sleep. In studies of sleep and ADHD, subjective and objective measures are not always congruent [17]. Actigraphy has been widely used to assess sleep and has been validated against polysomnography with agreement rates for minute-by-minute sleep–wake identification >90 % [18]. Furthermore, it has been validated with, the gold standard of objective sleep measures, polysomnography [18, 19]. We evaluated the effects of three doses of each drug and placebo on sleep in a within-subject, double-blind, randomized, placebo-controlled trial utilizing actigraphy. We hypothesized that (1) both medications would shorten sleep; (2) higher doses would be associated with greater decrease of sleep duration regardless of the medication; and (3) amphetamine would have greater negative impact on sleep duration compared with dexamethylphenidate.

2 Methods

2.1 Participants

Sixty-five participants met the inclusion criteria and were enrolled in the study. Of these, 37 children and adolescents with ADHD between the ages of 10 and 17 years (mean 11.6, standard deviation [SD] 1.956) had sufficient sleep data and were included in the analysis. Sufficient sleep data was defined as having at least one sleep score for placebo and for each active medication. Participants were recruited from investigator's clinical practice, colleague referrals, and flyers. The Kiddie Schedule for Affective Disorders for School-Age Children—Present and Lifetime Version (K-SADS-PL) was used to diagnose ADHD and comorbid disorders. Exclusion criteria were (1) IQ lower than 75; (2) a history of drug or alcohol use in the last 3 months; (3) a positive urinary toxic screen; (4) a medical condition that contraindicates stimulant treatment (e.g. cardiovascular disease); (5) a history of sleep disorders that interfere with sleep measurements (such as sleep-disordered breathing or restless leg syndrome); and (6) comorbid bipolar disorder, psychosis, autism spectrum disorder or those taking psychotropic medication other than for the treatment of ADHD, such as antidepressants or antipsychotics.

Twenty-seven participants were male (73 %) and ten were female (27 %). Twelve participants met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for ADHD inattentive subtype (32.4 %) and 25 for the combined subtype (67.4 %). Comorbid disorders in the sample included oppositional defiant disorder ($n = 11$, 29.7 %), enuresis ($n = 3$, 8.1 %), generalized anxiety disorder ($n = 1$, 2.7 %) and separation anxiety ($n = 1$, 2.7 %).

A parent or guardian was required to give signed informed consent and all participating children provided assent. The consent and assent forms, study protocol, and advertisements for recruitment were reviewed and approved by the Institutional Review Board of the University of Illinois at Chicago.

2.2 Procedure

The children were treated with MAS and d-MPH in a double-blind, randomized, placebo-controlled, crossover, dose-response study with weekly switches as described by Stein et al. in 2011 [11]. At baseline, participants were assessed for a diagnosis of ADHD and comorbid conditions, received baseline measures, and were screened to determine if they met any exclusion criteria. After screening, there was a washout period of 2 days for those who were under stimulant treatment and 2 weeks for those treated with atomoxetine. This washout time was chosen since MPH has a half-life of 2.4 h, both in IR and ER formulations [20]. The effects of stimulants on behavior dissipate 4–6 h after the last dose [21]. They were then randomized to receive either d-MPH or MAS initially, with the dose increasing every week for 4 weeks. The doses were 10, 20, and 25/30 mg. Doses were in milligrams to simulate clinical practice [22]. The placebo period was randomized to occur at any week of treatment, except the week before the highest dose to increase tolerability. After the 4 weeks, participants were switched to the other medication for another 4 weeks of treatment. Participants were instructed to take the medication with breakfast every morning. The total

treatment time was 8 weeks. Figure 1 is an example diagram of a treatment schedule. Bedtime and wake-up times were not controlled for during weekdays and weekends in order to follow the habitual sleep pattern of children in their natural home environment with the purpose of maximizing ecological validity.

2.3 Measures

2.3.1 Actigraphy and Sleep Logs—Actigraphs (AW64 series) were worn each night and were used to assess participant's sleep patterns in their natural home environment. These computerized wristwatch-like devices collect data generated by movements. They are minimally invasive and allow sleep to be recorded reliably without interfering with the family's routine. One-minute epochs were used to analyze actigraphic sleep data. Bed-times and wake times were reported for each participant using sleep logs, and these times were used as the start and end times for the analyses. For each 1-min epoch, the total sum of activity counts was computed. If they exceeded a threshold (threshold sensitivity value = mean score in active period/45), then the epoch was considered waking. If it fell below that threshold, then it was considered sleep.

Actigraphic data were analyzed using sleep software (Actiware Sleep 3.4, Mini-Mitter), and included the following parameters: (a) bedtime—the time the child got into bed; (b) sleep start—the beginning of sleep; (c) sleep end—the end of sleep; (d) get-up time—the time the child got out of bed; (e) actual sleep time—the amount of time (in minutes) between sleep start and sleep end, scored as sleep according to the Actiware-Sleep algorithm; and (f) nocturnal awakenings—the number of times the participant woke up during the night, to assess sleep continuity.

Sleep start and sleep end were used as measures of sleep schedule, actual sleep time was used as a measure of average sleep duration, and sleep efficiency, sleep latency, sleep bouts and wake bouts (which are the time asleep and awake during the rest period, respectively) were used as measures of sleep continuity. Actual sleep time was used in the analyses, instead of estimated sleep (as provided in the sleep logs), as it is a more objective and precise measure

2.3.2 Sleep Questionnaires—The following questionnaires were used to screen patients for participation in the study.

The Pediatric Sleep Questionnaire (PSQ) [23] was used to screen children for primary sleep disorders, such as sleep-disordered breathing (SDB), snoring, and sleepiness. The measure contains a validated, reliable, 22-item SDB scale, including a 4-item subscale for snoring, and another for excessive daytime sleepiness. The cut-off score for inclusion was 0.33 (33 % answered positively). The questionnaire is completed by parents [23].

The Periodic Leg Movement Disorder (PLMD) questionnaire was used to exclude subjects with PLMD. This is a validated, reliable, 6-item scale measuring periodic limb movement symptoms. The cut-off score for inclusion was 0.33 (33 % answered positively).

The Children's Sleep Habits Questionnaire (CSHQ), a retrospective, 45-item parent questionnaire that has been used in a number of studies to examine sleep behavior in young children, was employed to assess sleep disorders. The CSHQ includes items relating to a number of key sleep domains, such as bedtime behavior, snoring, daytime sleepiness, parasomnias, and insomnia that comprise the major clinical sleep complaints in school-age children. A cut-off total score of 41 yields a sensitivity of 80 % and a specificity of 72 % [24]. The CSHQ is validated for children aged 4–10 years, but has been previously administered with adolescents as well [25]. There are no other validated parent-report questionnaires that assess the sleep habits of children above 10 years.

2.3.3 Clinical Measures—The DSM-IV ADHD Rating Scale (ADHD-RS) was also used in this study to assess baseline ADHD severity, as well as treatment outcome. The measure consists of 18 items assessing DSM-IV criteria for inattention and hyperactivity/impulsivity, and yields a total score as well as hyperactivity/impulsivity and inattention subscale scores [26]. The questionnaire has been validated in child populations within the US and Europe, with high inter-rater reliability and moderate to high validity when compared with other ADHD symptom scales [27].

The Clinical Global Impression-Severity (CGI-S) scale completed by a blinded clinician [28] was also employed in the study. It is a widely used measure of overall ADHD symptom severity, and consists of one item with a score ranging from 1 (*normal*) to 7 (among the most severely ill of patients). This scale is widely used in clinical trials and has demonstrated clinical utility [29].

The K-SADS-PL is a validated semi-structured diagnostic interview designed to assess the severity of symptomatology, as well as the current and lifetime history of the psychiatric disorder. Trained psychologists, or child and adolescent psychiatrists, interviewed both the parents and child, and provided summary ratings of current and lifetime symptoms as well as level of impairment [30].

2.4 Analyses

2.4.1 Descriptive Statistics—Demographic and clinical characteristics at baseline were recorded for all participants. Means and SDs were calculated for sleep measures at baseline and during each period of medication at different doses.

2.4.2 Comparing the Impact of Medication and Dose on Sleep—All hypotheses were examined using two-way analyses of variance (ANOVA) with two within-subject factors (medication and dose), and with sleep measures (sleep start time, sleep end time, and sleep duration) as the dependent variables. Missing data were imputed with last observation carried forward (LOCF) by repeating the measure from the previous, lower dose of the same medication. Subjects who did not have sleep measurements for each week after imputing were excluded from the analysis. When significant effects were found for either dose or for an interaction between medication and dose, pairwise comparisons were performed to determine where the differences were located. Dose was treated as a categorical variable during such comparisons, to facilitate analysis. The assumptions of normality and homogeneity of the variance were verified by examining residuals derived from the mixed-

effects models. Violations to the assumption of sphericity were corrected with the lower-bound correction. Post hoc comparisons were performed with a Bonferroni correction. Significant differences were set at a p -level of 0.05.

3 Results

3.1 Descriptive Results

Demographic and descriptive data of the study population are presented in Table 1. Data on previous treatment history were collected. Participants reported that 29.7 % were treatment naïve, 45.9 % were treated previously with MPH, 5.4 % were treated with amphetamines, and 18.9 % were treated with atomoxetine. Comparisons between those who were included and excluded from the study revealed no significant differences in terms of treatment history ($\chi^2_{(3,65)} = 2.354$; $p < 0.05$) or treatment naïvety ($\chi^2_{(1,65)} = 0.39$; $p > 0.05$). There were also no significant differences in sleep duration between subjects with different treatment histories ($p > 0.05$) or treatment naïvety ($p > 0.05$). The severity of ADHD symptoms were compared between those included and excluded from the study due to missing sleep measurement data, and no significant differences were found between the groups ($F_{1,63} = 0.591$; $p > 0.05$). Age was analyzed as a factor and no significant effects were found ($p > 0.05$).

During placebo treatment, the mean duration of actual sleep was 459.6 min (SD 73.6). For both medications combined, the mean duration of actual sleep for 10, 20, and 25/30 mg, respectively, was 446.7 min (SD 63.58), 432.17 min (SD 64.6), and 425.5 min (SD 61.5), respectively. The mean duration for actual sleep during MAS treatment was 438.82 min (SD 67.2) and for d-MPH was 443.2 min (66.9).

The mean sleep start time during placebo treatment was 22:49 (SD 00:12:19). By dose, the mean sleep start times for 10, 20, and 25/30 mg of the stimulants were 23:04 (SD 00:10:40), 23:19 (SD 00:12:21), and 23:25 (SD 00:11:17), respectively. For MAS, the mean sleep start time was 23:09 (SD 00:11:05), and for d-MPH the mean time was 23:09 (SD 00:11:19). The mean sleep end time during placebo treatment was 07:42 (SD 00:15:36). By dose, the mean sleep end times for 10, 20, and 25/30 mg of the stimulants were 07:28 (SD 00:09:54), 07:35 (SD 00:10:46) and 07:32 (SD 00:11:09), respectively. For MAS, the mean sleep start time was 07:35 (SD 00:10:40), and for d-MPH the mean time was 07:34 (SD 00:10:04).

3.2 The Impact of Differing Doses on Sleep

To determine the impact of the dose of stimulant medications on sleep duration, ANOVA revealed a significant dose effect ($F_{(1,36)} = 9.560$; $p < 0.01$). Post hoc comparisons revealed significantly shorter sleep duration for participants receiving 20 and 30 mg compared with placebo and on 10 mg ($p < 0.05$). No significant differences were found in the post hoc comparisons. Table 2 shows the means and SDs of sleep duration for all doses. Figure 2 shows the means and standard errors of sleep duration for both medications at different doses. Table 3 shows the minimum, maximum, and mean reduction in minutes of sleep duration between significantly different doses.

The ANOVAs that were conducted to determine the impact of the dose of stimulant medications on sleep start time showed a significant dose effect ($F_{(1,36)} = 7.005$; $p < 0.05$). Post hoc contrasts showed a significantly later sleep start time on 20 or 30 mg doses compared with placebo ($p < 0.05$), regardless of stimulant medication. They also displayed significantly later sleep start times when comparing subjects receiving 30 mg with those receiving 10 mg ($p < 0.05$). There were no significant differences for the other contrasts. Figure 3 shows the means and standard errors of sleep start time for both medications at different doses on sleep start time. Means and SDs for sleep start time and sleep end time are presented in Table 2.

There were no significant differences in number of nocturnal awakenings between the different medications ($F_{(1,36)} = 1.786$; $p > 0.05$), nor were there any significant interactions between dose and medication ($F_{(1,36)} = 3.798$; $p > 0.05$).

3.3 The Impact of Dexmethylphenidate versus Mixed Amphetamine Salts on Sleep

There were no significant differences between the two stimulant medications on sleep duration ($F_{(1,36)} = 0.416$; $p > 0.05$), sleep start time ($F_{(1,36)} = 0.000$; $p > 0.05$), and sleep end time ($F_{(1,36)} = 0.004$; $p > 0.05$). Additionally, no significant interactions between stimulant medication and dose were found for sleep duration ($F_{(1,36)} = 2.183$; $p > 0.05$), sleep start time ($F_{(1,36)} = 2.736$; $p > 0.05$), and sleep end time ($F_{(1,36)} = 0.636$; $p > 0.05$). Table 2 shows the means and SDs of sleep duration and sleep schedule for both medications.

There were no significant differences in number of nocturnal awakenings between the different medications ($F_{(1,36)} = 1.786$; $p > 0.05$), nor were there any significant interactions between dose and medication ($F_{(1,36)} = 3.798$; $p > [0.05]$).

4 Discussion

The goal of this study was to compare the effect of two different stimulant medications and different doses of MAS and d-MPH on sleep schedule and sleep duration. We found that both medications were associated with decreased sleep duration. When the impact of medication doses on sleep were compared, sleep duration was shorter among those receiving the highest dose compared with placebo regardless of the medication. Analysis of the sleep schedule showed that this was due to a later sleep start time. There was a statistically significant mean reduction in sleep duration of 34 min between placebo and the highest dose (25 or 30 mg), as well as 21 min between the lowest dose (10 mg) and the highest dose. The mean sleep duration for the highest dose was 7 h and 5 min. The average effect on sleep was small, but may still be clinically significant for individual children. There was a non-significant trend between all doses towards shorter sleep durations with each increasing dose. No differences were found between MAS and d-MPH in sleep duration or schedule. Therefore, as far as sleep is concerned, at the group level there is no significant sleep benefit in using one medication over the other based upon objective measures.

Although higher doses were associated with improved efficacy in terms of ADHD symptoms, higher doses were also associated with negative effects on sleep [11]. There are numerous strategies that can be tried to reduce the impact of stimulants on sleep, including

behavioral treatments, switching medications, or combining stimulants with a sleep-promoting agent. Before considering these options, a common approach is to first either reduce the dose or switch to an IR agent with shorter duration, and then re-evaluate behavioral and sleep effects. Evidence for more severe sleep effect with ER versus IR stimulants is inconsistent, and there is marked variability between individuals in their response. Clinicians should recognize that a reduction in sleep duration is a risk in stimulant treatment of ADHD at higher doses. Sleep should be monitored in patients under stimulant treatment, and it may be beneficial to reduce the dose in patients to avoid the risk of shortened sleep duration. Augmentation with behavior therapy for ADHD symptoms may also result in lower stimulant dose, as was found in the National Institute of Mental Health Multimodal Treatment Study [31].

Long-term sleep disturbances in children have been found to lead to impairments in brain development, neuronal damage, and decreased developmental potentials [32]. It is also possible that the cumulative impact of reducing sleep duration might increase ADHD symptoms and impairment over time as there is evidence that reductions in sleep duration affect neurobehavioural scores [12] in children and increases inattention scores in adolescents [33]. ADHD symptom scales and sleep duration during stimulant treatment was not compared in this study; however, a future study could look into this interaction.

Previous studies in adult participants have shown that the effects on sleep during stimulant treatment of ADHD have been variable, with some reporting improvement, some worsening, and some no effect [34]. As these studies were carried out in adults, the effects may be different in children and adolescents.

The main limitation of this study was the small sample size and the short-term duration of the trial. As yet, there is little prospective data on sleep other than acute effects during short-term studies. The impact of cumulative effects on sleep in treated ADHD youth are known, although the present study suggests that ADHD youth treated with higher doses are at increased risk of partial cumulative sleep deprivation. While this does reduce the statistical power to detect changes, the sample size is similar to another study with objective sleep measures in a clinical ADHD population [35]. Future studies with a larger sample size and longer duration might be able to detect the significance of smaller reductions in sleep duration between similar doses. Another limitation to this study is the brief duration of each treatment dose (1 week). It is possible that the shortening effect of stimulants on sleep duration is transient and sleep duration will return to normal after a longer treatment period. The possibility of a rebound effect after treatment with stimulants was not monitored. According to recent literature, there appears to be a rebound effect, but it only significantly affects 10 % of those under stimulant treatment [36]. Future studies should consider controlling for acute withdrawal effects. In addition, a reliance on parental reports of adolescents' sleep via sleep questionnaires may be a limitation to this study; however, it was considered best to maintain a consistent procedure for all participants (i.e. children and adolescents).

While the within-subject comparisons provide control for individual response to medication, it can also lead to patients being excluded if they did not complete measurements for every

week. To prevent a bias from nonrandom exclusion due to incomplete measures, LOCF was used to impute data. This method is commonly used in clinical studies to replace missing data. In this case, LOCF leads to underestimating the differences between doses, so any significant findings are not due to the use of this method.

The Actiwatch was worn at home by the participants, and therefore provided measurements in an environment closer to real, day-to-day conditions as opposed to sleep measurements recorded in an artificial sleep setting (such as in a sleep clinic). However, in using this methodology there is also less control over the participants' behaviors, and compliance is more dependent on the participants themselves and their parents. Weekday and weekend differences in sleep duration and schedule were not compared due to a lack of viable sleep data. Sleep behavior may change due to school demands and, as such, this might have affected results. It may be possible to increase compliance with more frequent reminders between check-ups to properly wear the recording device. In this study, participants did not receive reminders between the weekly visits. An additional strength of this study was that the use of an objective measurement for sleep increases reliability for measures of sleep duration; the alternative use of subjective sleep measures tends to underestimate changes in sleep duration [19].

5 Conclusions

Overall, both ER MAS and ER d-MPH were associated with significant, dose-dependent reductions in sleep duration. Higher doses were associated with shorter sleep durations due to later sleep initiation times. There were no differences between the two long-acting MPH and amphetamine medications. Future studies with a larger sample size may elucidate smaller differences between doses, as well as moderators or predictors of sleep effects, which may improve dose optimization strategies.

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Key Points

Sleep problems have been found in patients with attention-deficit hyperactivity disorder (ADHD) and have been reported as side effects of stimulant treatment.

In this study, children with ADHD treated with higher doses of stimulants had a shorter sleep duration compared with children treated with lower doses.

To prevent sleep problems it may be beneficial to use lower doses of stimulants.

Fig. 1.

Example of a treatment schedule. Each treatment modality lasts for 1 week, for a total of 8 weeks. *MAS* mixed amphetamine salts, *d-MPH* dexamethylphenidate

Fig. 2. Sleep duration for MAS and d-MPH at all doses. Mean sleep duration decreases with higher doses for both medications. There are significant differences in mean duration during both placebo (asterisk) and 10-mg treatment (*double asterisk*) compared with 20 and 30 mg treatment ($p < 0.05$). MAS mixed amphetamine salts, d-MPH dexamethylphenidate

Fig. 3.

Sleep schedule: sleep start time for MAS and d-MPH at all doses. Mean sleep start time occurs later with higher doses for both medications. There are significant differences in mean sleep start time during placebo compared with 20- and 30-mg treatment ($p < 0.05$) [asterisk]. There was also a significant difference between 10-mg treatment and 30-mg treatment ($p < 0.05$) [double asterisk]. MAS mixed amphetamine salts, *d-MPH* dexamethylphenidate

Table 1

Demographic and clinical characteristics of study participants

Variables	Mean $\pm$ SD
Age (years)	11.60 $\pm$ 1.95
Weight (kg)	44.40 $\pm$ 14.40
Height (cm)	152.04 $\pm$ 13.07
BMI	19.43 $\pm$ 4.65
ADHD-RS	40.08 $\pm$ 9.43
CGI-S	5.03 $\pm$ 0.76
CSHQ total	49.53 $\pm$ 9.99
Bedtime resistance	8.31 $\pm$ 3.18
Sleep-onset delay	1.81 $\pm$ 3.19
Sleep duration	5.09 $\pm$ 1.87
Sleep anxiety	4.91 $\pm$ 2.19
Night wakings	3.97 $\pm$ 1.50
Parasomnias	8.51 $\pm$ 2.56
Sleep-disordered breathing	3.14 $\pm$ 1.14
Daytime sleepiness	15.31 $\pm$ 3.92
Gender [<i>N</i> (%)]	
Male	27 (73)
Female	10 (27)
ADHD subtype [<i>N</i> (%)]	
Inattentive	12 (32.4)
Combined	25 (67.4)

SD standard deviation, *BMI* body mass index, *ADHD-RS* Attention-Deficit Hyperactivity Disorder Rating Scale, *CGI-S* Clinical Global Impression-Severity, *CSHQ* Children's Sleep Habits Questionnaire

Table 2

Sleep duration and schedule by medication and dose

Dose	Mean		
	Sleep duration (min $\pm$ SD)	Sleep start time ($\pm$ SD)	Sleep end time ($\pm$ SD)
Placebo	459.6 $\pm$ 73.7	22:49 $\pm$ 00:12:19	07:42 $\pm$ 00:15:36
10 mg	446.7 $\pm$ 63.6	23:04 $\pm$ 00:10:40	07:28 $\pm$ 00:09:54
20 mg	432.2 $\pm$ 64.6	23:19 $\pm$ 00:12:21	07:35 $\pm$ 00:10:46
30 mg	425.6 $\pm$ 61.5	23:25 $\pm$ 00:11:17	07:32 $\pm$ 00:11:09
Medication			
MAS	438.821 $\pm$ 67.2	23:09 $\pm$ 00:11:05	07:35 $\pm$ 00:10:40
d-MPH	443.218 $\pm$ 66.9	23:09 $\pm$ 00:11:19	07:34 $\pm$ 00:10:04

SD standard deviation, MAS mixed amphetamine salts, *d*-MPH dexamethylphenidate

Table 3

Reduction in minutes of sleep duration in significantly different doses

Doses compared	Minimum	Maximum	Mean $\pm$ SD
Placebo vs. 20 mg	-124.37	197.00	27.44 $\pm$ 55.13
Placebo vs. 25 or 30 mg	-115.09	139.09	34.03 $\pm$ 51.79
10 mg vs. 25 or 30 mg	-25.13	90.66	21.14 $\pm$ 29.15

SD standard deviation