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Effect of Aptensio XR (Methylphenidate HCl Extended-Release) Capsules on Sleep in Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: To evaluate measures of sleep (exploratory endpoints) in two pivotal studies of a multilayer bead extended-release methylphenidate (MPH-MLR) treatment of attention-deficit/hyperactivity disorder in children.

Methods: Study 1 evaluated the time course of response to MPH-MLR ($n = 26$) patients in an analog classroom setting through four phases: screening (≤ 28 days), open label (OL) dose optimization (4 weeks), double-blind (DB) crossover (2 weeks; placebo vs. optimized dose), and follow-up call. Study 2 was a forced-dose parallel evaluation of MPH-MLR ($n = 230$) in four phases: screening (≤ 28 days), DB (1 week; placebo or MPH-MLR 10, 15, 20, or 40 mg/day), OL dose optimization (11 weeks), and follow-up call. Sleep was evaluated by parents using the Children's or Adolescent Sleep Habits Questionnaire (CSHQ or ASHQ) during the DB and OL phases. DB analysis: Study 1 (crossover), analysis of variance; Study 2, analysis of covariance. OL analysis: paired *t*-test.

Results: DB: treatments were significantly different in Study 1 only for CSHQ Sleep Onset Delay (MPH-MLR, 1.90 vs. placebo, 1.34; $p = 0.0046$, placebo was better), and Study 2 for CSHQ Parasomnias (treatment, $p = 0.0295$), but no MPH-MLR treatment was different from placebo (pairwise MPH-MLR treatment to placebo, all $p \geq 0.170$). OL: CSHQ total and Bedtime Resistance, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, and Sleep-disordered Breathing subscales decreased (improved, Study 1) significant only for CSHQ Night Wakings ($p < 0.05$); in Study 2 CSHQ total and Bedtime Resistance, Sleep Duration, Night Wakings, Parasomnias, and Daytime Sleepiness, and ASHQ total, Bedtime, Sleep Behavior, and Morning Waking all significantly improved ($p < 0.05$).

Conclusions: In both studies, there was minimal negative impact of MPH-MLR on sleep during the brief DB phase and none during the longer duration OL phase. Some measures of sleep improved with optimized MPH-MLR dose.

Keywords: ASHQ, CSHQ, extended-release methylphenidate, MPH-MLR, sleep

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Introduction

CHILDREN, ADOLESCENTS, and adults with attention-deficit/hyperactivity disorder (ADHD) frequently present with a variety of sleep-related difficulties before receiving ADHD medications (Stein et al. 2012; Kidwell et al. 2015). The impact of ADHD medications on sleep has been debated, with some studies showing deleterious effects on sleep, some studies showing minimal effects on sleep, and other studies showing improvement in sleep parameters after treatment with ADHD medications (Kidwell et al. 2015). The potential for different ADHD medications with varying pharmacokinetic profiles to have different impacts on sleep parameters also has been a topic of research and clinical discussion.

Forty to fifty percent of parents report sleep-related problems in their children with ADHD, particularly resistance to bedtime and/or delayed sleep onset (Owens 2009). When studies comparing children with ADHD with controls were evaluated, it was noted that children with ADHD had higher scores for bedtime resistance, sleep latency, morning awakening challenges, nighttime awakenings, sleep-disordered breathing, and daytime sleepiness (Cortese et al. 2009). Complicating the matter further is that many children with ADHD have comorbid psychiatric conditions, such as anxiety or depression, which also may affect sleep (Mayes et al. 2009; Accardo et al. 2012).

A population-based ADHD study conducted by the Australian government found that children with ADHD with insomnia had significantly worse psychosocial outcomes, missed more days of school, and their parents also missed more days of work (Sung et al. 2008). Primary sleep disorders coexisting with ADHD such as sleep-related movement disorders (Walters et al. 2008), circadian sleep disorders (Chiang et al. 2010; Gruber et al. 2012), and sleep-related breathing disorders (Cortese et al. 2006) often further complicate the sleep challenges in children and adolescents with ADHD.

Clinically, children and adolescents with insufficient or poor quality sleep often demonstrate behaviors of inattention and hyperactivity that may be misinterpreted as symptoms of ADHD (Owens 2009; Cassoff et al. 2012; Hvolby 2015; National Sleep Foundation 2015). In contrast to adults who generally exhibit fatigue and sleepiness in the face of insufficient or disrupted sleep, children's behavioral response to subjective sleepiness may manifest as increased activity levels as well as behavioral and mood dysregulation (Owens 2009).

Further complicating these relationships is the potential impact of ADHD stimulant medications on sleep. A recent meta-analysis of articles in which stimulants were used for ADHD found that worsening sleep latency was seen in some patients receiving stimulants and that this finding was more common in patients receiving more frequent stimulant dosing (Kidwell et al. 2015). Extended-release stimulant formulations given once daily had less impact on sleep latency than thrice-daily immediate-release dosing. These researchers also found that patients receiving stimulants had poorer sleep efficiency (i.e., time asleep/time in bed) than patients not receiving stimulants. This effect appeared to be attenuated with prolonged dosing (Kidwell et al. 2015).

Several clinical trials of long-acting stimulant medication have now examined sleep outcomes as a secondary outcome. Most of these studies have used subjective measures such as parent report. A study of the impact of OROS® methylphenidate (Janssen Pharmaceuticals, Inc., Titusville, NJ) on sleep using the Children's Sleep Habits Questionnaire (CSHQ) demonstrated improvement in parasomnias and no overall effect on sleep onset latency, although there was worsening in those children who had sleep complaints

(Kim et al. 2010). This study also used the objective measure polysomnography and found an increase in stage 2 sleep and improvement in the number of awakenings.

A study of the impact of lisdexamfetamine on sleep in children using the objective measures polysomnography and actigraphy as well as subjective parent report did not find any statistically significant increase in the primary endpoint of latency to persistent sleep on any of the three measures (Giblin and Strobel 2011). Subjective sleep measure results indicated the possibility that responses are influenced by sleep hygiene counseling before and throughout the study. These studies demonstrate that assessment of sleep as an outcome in its own right, as opposed to looking at sleep as an adverse event may provide us with a better understanding of the specifics of both the benefit and risk of stimulant treatment to children, facilitate the identification of children at risk, and identify the specific objective and subjective sleep parameters that may be impacted.

Aptensio XR® (Rhodes Pharmaceuticals L.P., Coventry, RI) is a multilayer bead extended-release methylphenidate (MPH-MLR) capsule formulation, in which each bead has 40% of the MPH located in the immediate-release outer layer and 60% of the methylphenidate located in a pH-dependent extended-release layer (Aptensio XR™ prescribing information 2015). Administration of MPH-MLR results in a biphasic pattern of methylphenidate plasma concentration with an initial peak at 2 hours postdose, gradually declining concentration over the next 4–6 hours, and a secondary peak ∼8 hours postdose with gradually declining concentration thereafter (Fig. 1) (Adjei et al. 2014; Aptensio XR™ prescribing information 2015).

In an analog classroom study (Study 1), significant improvements in ADHD symptoms were observed 1 hour after administration of MPH-MLR and sustained for ≥12 hours, with no diminution of effect (Wigal et al. 2014). The pivotal studies supporting marketing approval for MPH-MLR demonstrated that it is efficacious for ADHD in children and adolescents, as evaluated in both analog classroom and outpatient environments (Wigal et al. 2014, 2015).

Assessment of sleep was included in the design of the MPH-MLR pivotal studies as an exploratory endpoint to investigate the impact of MPH-MLR treatment on parent- and self-reported sleep
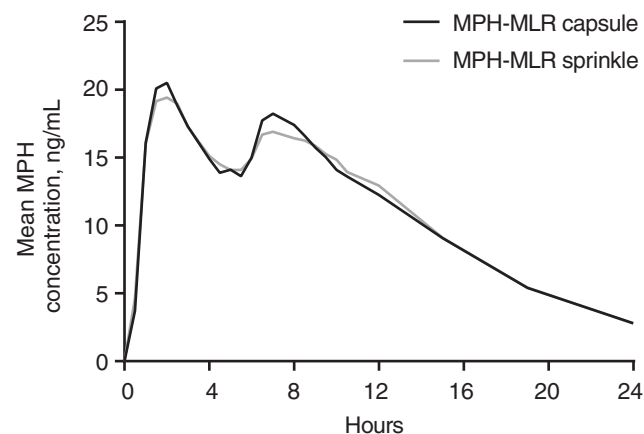

FIG. 1. Mean plasma MPH concentration versus time following a single dose of MPH-MLR capsule or sprinkles. MPH, methylphenidate; MPH-MLR, multilayer bead extended-release methylphenidate.

difficulties. We report the results of analyses of these endpoints to further the understanding of the impact of a long-acting methylphenidate preparation on parent-reported sleep.

Methods

Studies

Two randomized, double-blind (DB), placebo-controlled, phase 3 studies were included in the MPH-MLR clinical development program (Wigal et al. 2014, 2015). Study 1 (ClinicalTrials.gov Identifier: NCT01269463) evaluated the time course of response to MPH-MLR in an analog classroom setting (Wigal and Wigal 2006) and included four phases: screening (≤28 days), open label (OL) dose optimization (4 weeks), DB crossover (2 weeks), and follow-up call (Wigal et al. 2014). Children (male or female) aged 6–12 years at the time of consent with any of the three subtypes of ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) (American Psychiatric Association 2000) were eligible for inclusion in the study. Exclusion criteria included severe concurrent psychiatric or medical illness and functioning at an estimated intellectual level <80 on the Wechsler Abbreviated Scale of Intelligence.

During the OL dose-optimization phase, dosing was initiated with MPH-MLR 15 mg and titrated weekly over the next 2–4 weeks to an optimized dose of 15, 20, 30, or 40 mg. Patients were then randomized in a 1:1 ratio to one of two treatment sequence groups (optimized dose–placebo or placebo–optimized dose). The optimized dose or placebo was administered for 1 week, and the patient participated in an analog classroom study day and crossed over to the second treatment and participated in a second analog classroom day. The primary efficacy endpoint was the mean of the DB on-treatment postdose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-total scores over time points 1.0, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0 hours during the classroom day.

Study 2 (ClinicalTrials.gov Identifier: NCT01239030) was a fixed-dose evaluation of MPH-MLR safety/efficacy with the assigned dose given from day 1 with no titration. The four study phases included screening (≤28 days), DB (1 week), OL dose optimization (11 weeks), and follow-up call (Wigal et al. 2015). This study included children and adolescents (male and female) aged 6–18 years at the time of consent with an ADHD diagnosis as defined in the DSM-IV-TR. Exclusion criteria were similar to Study 1.

During the DB phase, patients were randomized (1:1:1:1:1) to receive MPH-MLR 10, 15, 20, or 40 mg, or placebo. During the 11-week OL dose-optimization phase, treatment was initiated with the once-daily MPH-MLR 10 mg dose and titrated (up or down) at weekly intervals until the optimal dose was achieved. MPH-MLR capsules of 10, 15, 20, 30, 40, 50, and 60 mg were available in the OL dose-optimization phase. The primary efficacy endpoint measure was the change from baseline to the end of the DB phase in the clinician-rated ADHD Rating Scale-IV total score.

All participants and/or legal guardians provided written informed consent in both studies before receiving pre-enrollment, psychiatric and medical evaluations. Both studies were conducted in compliance with Good Clinical Practice guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, the United States Code of Federal Regulations that relate to clinical trial conduct, and the principles of the Declaration of Helsinki. Further study details for Studies 1 and 2 have been published elsewhere (Wigal et al. 2014, 2015).

In both studies, sleep was evaluated in children aged 6–12 years using the parent-reported CSHQ as well as the child-reported Sleep Self-Report (SSR). For adolescents aged 13–18 years, modified versions of the Adolescent Sleep Habits Questionnaire (ASHQ; parent report and self-report) were used. In Study 1, sleep assessments were collected at baseline, the end of OL dose-optimization phase (beginning of the DB phase), and weekly during the DB crossover phase. In Study 2, sleep assessments were collected at the beginning and end of the DB phase and again at the end of the OL dose-optimization phase.

Assessments

The CSHQ is a retrospective 48-item parent questionnaire used to examine sleep behavior that has been validated in young children (aged 4–10 years) (Owens et al. 2000b). It includes items relating to a number of key sleep domains that encompass the major presenting clinical sleep complaints in this age group. Parents are asked to recall sleep behaviors occurring over a typical recent week and to rate the behavior on a three-point scale scored 1–3, with a higher score indicative of more problems.

Ratings for most items were as follows: "usually" if something occurred 5–7 times in a week, "sometimes" if it occurred 2–4 times in a week, or "rarely" if something occurred 0–1 time in a week. Two items required the rating to be "not sleepy," "very sleepy," or "falls asleep." Thirty-three items were grouped into eight subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep-Disordered Breathing, and Daytime Sleepiness. Scale scores were the sum of the scores for items in the scale. If an item from a scale was not rated, the scale score was taken as missing.

The SSR is a 26-item questionnaire that has been used in previous studies (Owens et al. 2000a, 2000c) to measure sleep disturbances reported by children themselves. Twenty-three items were grouped into three subscales for this analysis: Bedtime, Sleep Behavior, and Daytime Sleepiness. Scoring of items and scales mirrored the parent-reported version.

The ASHQ was developed to parallel the parent- and self-reported versions of the CSHQ and examines sleep behavior in adolescents (aged 13–18 years); its structure is similar to the CSHQ. The ASHQ-Parent version was administered by clinicians and directed to parents. For each item there were four possible responses (never = 0 ×/ week; rarely = 1–2 ×/week; sometimes = 3–5 ×/week; usually = 6–7 ×/week). Items were grouped into the following six subscales: Bedtime, Sleep Behavior, Waking During the Night, Morning Waking, Sleep Habits, and Daytime Sleepiness. Item scores ranged from 0 to 3, with higher scores more indicative of sleep problems. In this study, the ASHQ was modified to include a response of "don't know." Scoring was taken as the mean of the nonmissing data times the number of items in the scale because of "don't know" responses. The clinician administered a slightly different version of the ASHQ to adolescents (ASHQ-Self). ASHQ-Self scoring and groupings were similar to the ASHQ-Parent report.

Analysis

In Study 1, the observed DB data were analyzed using an analysis of variance appropriate for a crossover study with terms for subject, treatment, period, and sequence. In Study 2, the change during the DB phase was analyzed using an analysis of covariance appropriate for a parallel study with terms for treatment and site and with each patient's baseline score as a covariate with a pairwise comparison of

each MPH-MLR treatment to placebo using Dunnett's test. In both studies, the analysis of the OL dose-optimization phase in each study was a paired *t*-test comparing the start of study with the end of the OL dose-optimization phase. All *p*-values were two sided.

Results

Patient demographics

Study 1 included 26 patients who completed screening and received at least one dose of study drug and 20 patients who completed SKAMP assessments for all study time points and received the scheduled treatments (Wigal et al. 2014). At screening, two patients were receiving psychotropic medication. The mean (standard deviation [SD]) optimized dose of MPH-MLR was 25.7 (6.2) mg. Study 2 included 230 patients who completed screening and received at least one dose of study drug, and 221 children and adolescents who completed the ADHD Rating Scale-IV assessments on days 0 and 7 (Wigal et al. 2015). At screening, 74 patients were receiving psychotropic medication.

In Study 2, the mean (SD) optimized dose of MPH-MLR was 36.6 (12.8) mg or 0.93 (0.47) mg/kg. The relationship between optimized dose and weight was not statistically significant (linear regression, slope, $p = 0.1049$). In the DB phase, mean MPH-MLR mg/kg doses were as follows: 10 mg (0.27 mg/kg), 15 mg (0.41 mg/kg), 20 mg (0.52 mg/kg), and 40 mg (0.89 mg/kg). In each study, the population was largely white (81% in Study 1, 69% in Study 2) and the majority of patients were male (54% in Study 1, 67% in Study 2) (Wigal et al. 2014, 2015). At study entry, there was evidence of sleep impairment (Table 1).

Study 1

During the 4-week OL dose-optimization phase, scores decreased (improved) from baseline for CSHQ total score and Bedtime Resistance, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, and Sleep-Disordered Breathing subscale scores, although the improvement was only significant for Night Wakings (Table 2). Scores increased (worsened) for Sleep Onset Delay and Daytime Sleepiness subscale scores, but neither was significant. Individual Sleep Onset Delay subscale scores showed that 66.7% (16/24) of patients had no change, 20.8% (5/24) worsened, and 12.5% (3/24) improved. SSR total score and Bedtime and Daytime Sleepiness subscale scores also improved, while Sleep Behavior subscale score worsened, but none reached statistical significance.

During the 2-week DB crossover phase, CSHQ ratings for the Sleep Onset Delay subscale were significantly higher (worse) for

TABLE 1. INITIAL ASSESSMENTS[a] OF SLEEP IN THE MULTILAYER BEAD EXTENDED-RELEASE METHYLPHENIDATE PHASE 3 STUDIES

	Study 1 (n = 26)	Study 2
Mean (SD) CSHQ total score		
Parent	49.1 (10.10)	46.9 (7.84), n = 130
Mean (SD) ASHQ total score		
Parent	NA	44.8 (13.96), n = 74

CSHQ scores >41 are indicative of a sleep disorder (Owens et al. 2000b).
[a]Beginning of the study.
ASHQ, Adolescent Sleep Habits Questionnaire; CSHQ, Children's Sleep Habits Questionnaire; NA, not applicable (only children aged ≤12 years included in study); SD, standard deviation.

TABLE 2. CHANGE IN SLEEP SCORES DURING THE 4-WEEK OPEN-LABEL DOSE-OPTIMIZATION PHASE (STUDY 1; N = 24)

	Mean (SD) decrease	p[a]
CSHQ-Parent		
Total	2.1 (7.87)	0.2074
Bedtime Resistance	1.0 (2.51)	0.0538
Sleep Onset Delay	−0.1 (0.68)	0.3769
Sleep Duration	0.2 (2.04)	0.6921
Sleep Anxiety	0.6 (1.69)	0.0830
Night Wakings	0.5 (0.93)	0.0243
Parasomnias	0.5 (1.38)	0.0674
Sleep-Disordered Breathing	0.1 (0.45)	0.1853
Daytime Sleepiness	−0.3 (3.29)	0.7129
SSR		
Total	1.2 (5.70)	0.3100
Bedtime	1.0 (3.39)	0.1617
Sleep Behavior	−0.3 (2.15)	0.5748
Daytime Sleepiness	0.5 (2.30)	0.3397

[a]*p*-Values are from paired *t*-test for the change from study start to end of the open-label phase.
CSQH, Children's Sleep Habits Questionnaire; SD, standard deviation; SSR, Sleep Self-Report.

optimized MPH-MLR dose than placebo (1.9 vs. 1.34, respectively; $p = 0.0046$; Table 3), while CSHQ total score and other subscales were not significantly different between placebo and optimized MPH-MLR dose. Individual patient scores for the Sleep Onset Delay subscale showed that MPH-MLR and placebo scores were not different for 60% (12/20) of patients and indicated more problems (higher score) for 40% (8/20) of patients. SSR score for the DB phase did not show any statistically significant difference between placebo and optimized dose for the SSR total or any subscale scores (Table 2).

TABLE 3. SLEEP SCORES DURING THE 2-WEEK DOUBLE-BLIND CROSSOVER PHASE (STUDY 1; EVALUABLE POPULATION; N = 20)

	LS mean		p[a]
	MPH-MLR	Placebo	Treatment
CSHQ-Parent			
Total	46.5	44.4	0.1466
Bedtime Resistance	9.1	8.8	0.5342
Sleep Onset Delay	1.9	1.3	0.0046
Sleep Duration	4.6	4.0	0.1282
Sleep Anxiety	5.4	5.4	0.8885
Night Wakings	3.7	3.5	0.3955
Parasomnias	8.2	8.1	0.4973
Sleep-Disordered Breathing	3.2	3.2	0.6548
Daytime Sleepiness	13.4	12.9	0.3052
SSR			
Total	39.9	41.2	0.2507
Bedtime	21.1	21.5	0.5642
Sleep Behavior	11.3	11.8	0.4142
Daytime Sleepiness	7.5	7.9	0.1992

[a]Mixed-effects analysis of variance, fixed terms for treatment, period, and sequence; random term for subject within sequence.
CSHQ, Children's Sleep Habits Questionnaire; LS, least-squares; MPH-MLR, multilayer bead extended-release methylphenidate; SSR, Sleep Self-Report.

Safety data from Study 1 also were reviewed for sleep-related adverse events. Insomnia was reported as an adverse event by 30.8% (8/26) of patients in the OL dose-optimization phase and 0.0% (0/21) and 4.5% (1/22) of patients receiving MPH-MLR or placebo, respectively (DB crossover phase). Discontinuations related to insomnia were few: None during the DB phase and only one of four discontinuations during the OL dose-optimization phase.

Study 2

During the initial 1-week DB fixed-dose phase, there was no significant difference among treatments for CSHQ total or any subscale except for Parasomnias (Table 4). For the Parasomnias subscale score, p-values from Dunnett's multiple comparison follow-up comparison of each MPH-MLR treatment with placebo were significant only for the 10 mg dose ($p=0.0170$ [10 mg], $p=0.9071$ [15 mg], $p=0.9674$ [20 mg], $p=0.2338$ [40 mg]). There was no difference in Sleep Onset Delay subscale score during the DB phase, even with higher MPH-MLR doses. There were no significant treatment differences for changes on the SSR or ASHQ-Parent or ASHQ-Self during the DB phase.

During the 11-week OL dose-optimization phase, mean total and all subscale scores decreased from baseline (fewer sleep-related problems) for the CSHQ, SSR, and ASHQ-Parent, and most subscale scores were significant (Table 5). At end of OL, CSHQ scores were significantly lower for the following: total score and Bedtime Resistance, Sleep Duration, Night Wakings, Parasomnias, and Daytime Sleepiness subscale scores. ASHQ-Parent total score and Bedtime, Sleep Behavior, and Morning Waking subscale scores were also significantly lower at the end of OL dose optimization. For the ASHQ-Self, all scales decreased significantly, except for the Sleep Habits and Bedtime subscales, which decreased, but not significantly. During the OL dose-optimization phase, CSHQ Sleep Onset Delay subscale score did not change in 59.6% (81/136) of patients, worsened in 16.2% (22/136) of patients, and improved in 24.3% (33/136) of patients.

During the 1-week, DB phase, insomnia was reported as an adverse event by 9.8% (18/183) and 2.1% (1/47) of patients receiving MPH-MLR or placebo, respectively. The rate of reported insomnia did not appear to increase as dose increased: 10 mg (5/49 [10.2%]), 15 mg (2/44 [4.5%]), 20 mg (6/45 [13.3%]), and 40 mg (5/45 [11.1%]). During the OL dose-optimization phase, 11.8% (26/221) of patients reported insomnia as an adverse event. In the

TABLE 4. CHANGE IN SLEEP SCORES DURING THE 1-WEEK DOUBLE-BLIND PHASE (STUDY 2; EVALUABLE POPULATION; $N=221$)

| | LS mean decrease | | | | | p^a |
	MPH-MLR 10 mg	MPH-MLR 15 mg	MPH-MLR 20 mg	MPH-MLR 40 mg	Placebo	Treatment
CSHQ						
Total ($n=124$)	−0.2	1.2	0.9	1.7	1.5	0.5184
Bedtime Resistance	−0.2	0.1	−0.2	0.3	0.2	0.5214
Sleep Onset Delay	0.1	0	−0.1	−0.1	0	0.7900
Sleep Duration	−0.2	0	−0.3	0	0	0.9476
Sleep Anxiety	−0.2	0.2	0.1	0	0.1	0.4236
Night Wakings	0.1	0.1	0.1	0	0	0.9859
Parasomnias	−0.2	0.5	0.6	0.1	0.7	0.0295
Sleep-Disordered Breathing	−0.1	0.1	0	0	0.1	0.4216
Daytime Sleepiness	0.1	0.6	0.6	1.2	0.6	0.5483
SSR						
Total ($n=135$)	−0.7	1.0	2.5	1.1	0.4	0.1604
Bedtime	−0.3	0.5	1.1	0.3	0.7	0.4904
Sleep Behavior	0	0.2	0.1	0.3	0	0.9743
Daytime Sleepiness	−0.1	0.4	0.7	0.4	0	0.2289
ASHQ-Parent						
Total ($n=74$)	0.9	4.5	3.9	4.9	0.9	0.4485
Bedtime	0	1.8	1.1	1.5	−0.7	0.2482
Sleep Behavior	0.4	0	1.1	1.2	0.6	0.8334
Waking During the Night	0.4	0.9	0.9	0.7	0.7	0.9528
Morning Waking	−0.2	0.2	0.1	0	0.1	0.9978
Sleep Habits	−0.5	0.1	0.1	0.5	−0.4	0.4594
Daytime Sleepiness	0.5	0.3	1.3	0.7	0.4	0.9418
ASHQ-Self						
Total ($n=71$)	2.9	10.4	4.5	5.8	3.2	0.3219
Bedtime	1.0	0.8	0.6	1.1	0.8	0.9966
Sleep Behavior	0.8	1.5	1.2	1.4	0.8	0.9677
Waking During the Night	0	1.5	0.4	0.6	0.9	0.4306
Morning Waking	0.8	2.0	0.3	0.9	1.1	0.7464
Sleep Habits	−0.2	−0.6	0.6	−0.2	−0.4	0.1845
Daytime Sleepiness	0.8	1.6	2.1	1.8	0.2	0.1853

[a]Analysis of covariance model has fixed terms for treatment and sites; covariate is baseline score. Sites with <10 patients combined.

ASHQ, Adolescent Sleep Habits Questionnaire; CSHQ; Children's Sleep Habits Questionnaire; LS, least-squares; MPH-MLR, multilayer bead extended-release methylphenidate; SSR, Sleep Self-Report.

TABLE 5. CHANGES IN SLEEP SCORES DURING THE 11-WEEK OPEN-LABEL DOSE-OPTIMIZATION PHASE (STUDY 2)

	n	Mean (SD) decrease[a]	p[b]
CSHQ-Parent			
Total	122	3.5 (6.44)	<0.001
Bedtime Resistance	128	0.5 (1.72)	0.0013
Sleep Onset Delay	136	0.1 (0.89)	0.1037
Sleep Duration	132	0.4 (1.64)	0.0141
Sleep Anxiety	129	0.2 (1.34)	0.1698
Night Wakings	129	0.2 (1.16)	0.0296
Parasomnias	126	0.7 (1.75)	<0.0001
Sleep-Disordered Breathing	129	0.1 (0.56)	0.0858
Daytime Sleepiness	132	1.5 (3.42)	<0.0001
SSR			
Total	129	2.2 (6.18)	<0.0001
Bedtime	134	1.0 (4.02)	0.0056
Sleep Behavior	134	0.8 (2.60)	0.0008
Daytime Sleepiness	133	0.6 (1.74)	0.0001
ASHQ-Parent			
Total	69	6.5 (12.26)	<0.0001
Bedtime	69	1.2 (4.40)	0.0240
Sleep Behavior	69	1.4 (3.50)	0.0016
Waking During the Night	69	0.4 (2.46)	0.1398
Morning Waking	69	1.7 (3.59)	0.0002
Sleep Habits	69	0.3 (1.79)	0.1471
Daytime Sleepiness	69	1.0 (4.67)	0.0805
ASHQ-Self			
Total	67	5.2 (11.53)	0.0004
Bedtime	67	0.9 (4.05)	0.0731
Sleep Behavior	67	1.1 (3.23)	0.0081
Waking During the Night	67	0.9 (2.45)	0.0033
Morning Waking	67	1.4 (3.81)	0.0031
Sleep Habits	67	−0.2 (2.42)	0.5668
Daytime Sleepiness	67	1.0 (4.05)	0.0505

[a]Decrease from beginning of the study to end of the OL phase or early termination in the OL phase.
[b]From paired t-test.
ASHQ, Adolescent Sleep Habits Questionnaire; CSHQ; Children's Sleep Habits Questionnaire; OL, open label; SD, standard deviation; SSR, Sleep Self-Report.

DB phase, 11.1% (1/9) of patients discontinued owing to insomnia. In the OL dose-optimization phase, 19.0% (4/21) of patients discontinued owing to insomnia.

Discussion

The results of these studies suggest that while MPH-MLR, an extended-release methylphenidate, negatively impacted some dimensions of sleep such as sleep onset latency, it also had beneficial effects on other dimensions of sleep. Previous research has focused predominantly on psychostimulant-associated ''insomnia'' as an adverse event loosely defined by the investigator, which is often not further differentiated as difficulty with sleep onset or sleep maintenance. These differences in insomnia definition may account for the apparent discrepancy between no change or improvements in CSHQ sleep parameters and rates of reported insomnia adverse events during the longer study phases (dose-optimization phase in Study 1 and OL phase in Study 2).

The finding in this study that stimulant administration was associated with a delay in sleep onset compared with placebo is similar to a number of other studies of children with ADHD. As noted in the

introduction, a meta-analysis of studies that reported sleep data in patients treated with stimulants noted that patients themselves and/or parents of children or adolescents with ADHD more frequently report problems with prolonged sleep onset latency and decreased sleep efficiency (Kidwell et al. 2015).

Another meta-analysis of studies that used actigraphy (wristwatch-like device that captures and stores body movement data to approximate sleep/wake patterns) to monitor sleep effects found a significant impact of methylphenidate administration on total sleep time (decreased) (De Crescenzo et al. 2014). Both sleep onset latency and total sleep time were negatively impacted by methylphenidate administration in another study of 21 children aged 6–12 years (Corkum et al. 2008). In another 8-week randomized crossover study, 37 children aged 10–17 years received extended-release dexmethylphenidate and extended-release mixed amphetamine salts (Santisteban et al. 2014). Both medications decreased sleep duration as measured by actigraphy, and there was no significant difference between the two medications. Higher doses were associated with a later sleep onset and shorter sleep duration (Santisteban et al. 2014).

In contrast, our findings suggest that while improvement in sleep parameters, as evidenced by a decrease in total and subscale sleep survey scores, was generally not seen over the short duration of the DB phase in each of these studies, there also was no evidence that sleep deteriorated during this time. Furthermore, prolonged administration of MPH-MLR at an optimized dose in the OL phase of both studies appeared to result in some improvement in sleep parameters. As previously described, the possibility that administration of stimulants, including methylphenidate, might have a null or even beneficial effect on some aspects of sleep has been reported in the literature (Kim et al. 2010; Giblin and Strobel 2011).

Similar to the results of these studies, in a study of once-daily oral or transdermal methylphenidate, there was little evidence suggesting a negative impact of treatment on sleep parameters, particularly once an optimized dose was achieved (Faraone et al. 2009). A study of children in Thailand with ADHD aged 5–12 years found no significant differences in sleep difficulties in children who were receiving ADHD treatment with stimulants and those who were not (Chiraphadhanakul et al. 2015). An observational sleep study in children with ADHD reported little evidence that supported a substantial effect in objective or subjective measures of sleep (O'Brien et al. 2003); even a third dose of methylphenidate administered late in the day to children with ADHD did not appear to have a negative impact on sleep (Kent et al. 1995).

Finally, polysomnography data from children treated with OROS methylphenidate actually showed a significant decrease in the number of awakenings (Kim et al. 2010), and subjective measures in another study indicated that nighttime awakenings were improved in children with ADHD treated with thrice-daily methylphenidate (Sangal et al. 2006).

In general, subjective reports in these studies were consistent with objective findings, when available. In addition, these subjective measures provided information on parent experience of sleep in their children over time which is different from, but as important as, the objective impact on sleep itself. It is frequently the caregiver report that defines behaviors as a ''problem'' in the clinical setting and thus determines the level and type of recommended intervention.

The reasons that stimulants might be responsible for some improvements in sleep remain theoretical. It is possible that use of stimulants, at therapeutic levels that are sustained into the evening hours, would reduce ADHD symptoms just before and at bedtime. By

mitigating these symptoms, bedtime resistance might be attenuated, facilitating an easier transition to sleep and initiation of sleep itself.

This study has limitations that should be considered in the interpretation of results, some of which relate to measurement issues. Sleep assessment was not the primary objective of either Study 1 or Study 2, and these data are based on patient or parental report; thus, these findings may warrant further investigation with objective measures of sleep such as actigraphy or polysomnography. Studies have generally not demonstrated a correlation between subjective and objective assessments of sleep in children with ADHD (Corkum et al. 2001; Wiggs et al. 2005; Markovich et al. 2014), and it is likely that these various tools measure somewhat different sleep constructs.

Our main goal in this analysis was to assess the impact of MPH-MLR on clinically relevant practical sleep parameters, so we utilized parent- and self-reports as being most legitimately reflective of real-world parent and patient concerns. All the sleep measures were, however, consistently used at all time points in the studies and the results suggest considerable agreement between scales. In addition, the ASHQ-Parent and ASHQ-Self report used in these studies has not been fully validated; furthermore, children aged ≤12 years were included in this group and the CSHQ has only been validated in children aged ≤10 years.

It also should be noted that sleep was assessed by both the parent and the child/adolescent in the studies, and while the improvements in the total score were directionally similar, they were numerically larger when assessed by the parent. There was a discrepancy between some parent- and self-report scores; for example, in Study 1, parents noted a worsening on the Daytime Sleepiness subscale, while children reported an improvement. Similarly, adolescents in Study 2 reported a worsening on the Sleep Habits subscale, while parents reported an improvement. This underscores the importance of querying both children/adolescents and caregivers about sleep.

The DB phase was brief in both studies (active drug was administered for only 1 week). The forced dose randomization to five groups in Study 2, with children systematically over- and undermedicated, is not optimal for looking at drug versus placebo effects on insomnia. Finally, the OL design precludes ruling out unspecific factors such as rater bias and time effects. The argument might be made, for example, that response fatigue (i.e., caregivers being less likely to report problems as time goes on) may have been at least partially responsible for the apparent decrease in sleep symptoms observed during the OL phases. Not all sleep subscale scores declined over time, however, and interestingly, the Sleep-Disordered Breathing subscale, which would not be expected to be impacted by stimulant therapy, did not change significantly during the OL phase in either Study 1 or Study 2.

Children and adolescents with ADHD and sleep difficulties may benefit from receipt of information about healthy sleep practices (Weiss et al. 2006) as evidenced by two empirical trials (Hiscock et al. 2015; Corkum et al. 2016).

Conclusions

Overall, the results of these studies replicate previous findings suggesting that extended-release methylphenidate may be associated with short-term subjective reports of sleep onset delay in children and adolescents compared with placebo, but that these effects do not persist or worsen, and there may, in fact, be some improvements in sleep parameters over time, as evidenced by lower total and specific subscale scores during the OL phase on the CSHQ and ASHQ. The findings suggest that adverse sleep effects of stimulants, at least for some children with ADHD, may be transient in nature, and that improvement in ADHD daytime symptoms associated with stimulant administration may have a beneficial impact on sleep. Future studies should address these and other possible mechanisms for the differential effects of stimulants on sleep and sleep behavior in children with ADHD.

Clinical Significance

Overall, the results of this analysis of two studies replicate previous findings that suggest that extended-release methylphenidate may be associated with short-term subjective reports of sleep onset delay compared with placebo; however, the findings also suggest that these effects do not persist or worsen, and there may, in fact, be some improvements in sleep parameters over time. One potential mechanism for improvement in sleep parameters is that reduction in ADHD symptoms in the evening just before and at bedtime could reduce bedtime resistance and facilitate settling and sleep onset.

Disclosures

Dr. Owens is a consultant for Jazz, Pfizer, Purdue, Rhodes Pharmaceuticals L.P., Teva, and UCB, and has received research support from Jazz and UCB. Dr. Weiss is on the speakers bureau for Eli Lilly, Janssen, Purdue, and Shire, is a consultant for Purdue and Rhodes, and has received research support from Purdue. Dr. Nordbrock is a consultant for Rhodes Pharmaceuticals L.P. Dr. Mattingly is a speaker for Forest, Lundbeck, Merck, Otsuka, Shire, Sunovion, and Takeda, and has served as a consultant or performed research for Alcobra, Alkermes, Forest, Forum, Janssen, Lundbeck, Merck, Novartis, Noven, Otsuka, Pfizer, Purdue, Reckitt Benckiser, Rhodes Pharmaceuticals L.P., Shire, Sunovion, Takeda, and Vanda. Dr. Wigal is a consultant, advisory board member, and speakers bureau member for Attentiv, Eli Lilly, Ironshore, Neos, Neurovance, Next-Wave, Noven, NuTec, Pfizer, Purdue, Rho, Rhodes Pharmaceuticals L.P., Shionogi, Shire, Sunovion, Tris, and Vernalis, and has received grant/research support from Eli Lilly, Forest, Ironshore, the National Institutes of Health, Neurovance, NextWave, Noven, NuTec, Purdue, Rho, Rhodes Pharmaceuticals L.P., Shire, Sunovion, and Tris. Dr. Greenhill has received research support from the National Institute on Drug Abuse, the National Institutes of Health, and Shire, and is on the advisory board for BioBehavioral Diagnostics. Dr. Chang is a consultant for Rhodes Pharmaceuticals L.P. Dr. Childress has received research support from Alcobra, Arbor, Forest, Ironshore, Lilly, Lundbeck, Medgenics, Neos, Neurovance, NextWave, Noven, Otsuka, Pearson, Pfizer, Purdue, Rhodes Pharmaceuticals L.P., Shire, Sunovion, Theravance, and Tris; been a consultant for and received honoraria from Ironshore, Neos, Pfizer, Rhodes Pharmaceuticals L.P., and Shire; received travel support from Ironshore, NextWave, Pfizer, and Shire; has received writing assistance on projects from Arbor, Ironshore, Neos, NextWave, Pfizer, Rhodes Pharmaceuticals L.P., and Shire; received payment for lectures from Arbor, Pfizer, and Shire; and has been an advisory board member for Arbor, Ironshore, Neos, Neurovance, NextWave, Noven, Pfizer, and Rhodes Pharmaceuticals L.P. Drs. Kupper and Adjei are employees of Rhodes Pharmaceuticals L.P.

References

Accardo JA, Marcus CL, Leonard MB, Shults J, Meltzer LJ, Elia J: Associations between psychiatric comorbidities and sleep disturbances in children with attention-deficit/hyperactivity disorder. J Dev Behav Pediatr 33:97–105, 2012.

Adjei A, Teuscher NS, Kupper RJ, Chang W-W, Greenhill L, Newcorn JH, Connor DF, Wigal S: Single-dose pharmacokinetics of methylphenidate extended-release multiple layer beads administered as intact capsule or sprinkles versus methylphenidate immediate-release tablets (Ritalin®) in healthy adult volunteers. J Child Adolesc Psychopharmacol 24:570–578, 2014.

American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th ed. Text Revision. Washington, DC: American Psychiatric Association; 2000.

Aptensio XR™: (Methylphenidate Hydrochloride Extended-Release) Capsules [Prescribing Information]. Coventry, RI, Rhodes Pharmaceuticals L.P., 2015.

Cassoff J, Wiebe ST, Gruber R: Sleep patterns and the risk for ADHD: A review. Nat Sci Sleep 4:73–80, 2012.

Chiang H-L, Gau SS-F, Ni H-C, Chiu Y-N, Shang C-Y, Wu Y-Y, Lin L-Y, Tai Y-M, Soong W-T: Association between symptoms and subtypes of attention-deficit hyperactivity disorder and sleep problems/disorders. J Sleep Res 19:535–545, 2010.

Chiraphadhanakul K, Jaimchariyatam N, Pruksananonda C, Chonchaiya W: Increased sleep disturbances in Thai children with attention-deficit hyperactivity disorder compared with typically developing children. Behav Sleep Med 14:677–686, 2015.

Corkum P, Lingley-Pottie P, Davidson F, McGrath P, Chambers CT, Mullane J, Laredo S, Woodford K, Weiss SK: Better nights/better days-distance intervention for insomnia in school-aged children with/without ADHD: A randomized controlled trial. J Pediatr Psychol 41:701–713, 2016.

Corkum P, Panton R, Ironside S, Macpherson M, Williams T: Acute impact of immediate release methylphenidate administered three times a day on sleep in children with attention-deficit/hyperactivity disorder. J Pediatr Psychol 33:368–379, 2008.

Corkum P, Tannock R, Moldofsky H, Hogg-Johnson S, Humphries T: Actigraphy and parental ratings of sleep in children with attention-deficit/hyperactivity disorder (ADHD). Sleep 24:303–312, 2001.

Cortese S, Faraone SV, Konofal E, Lecendreux M: Sleep in children with attention-deficit/hyperactivity disorder: Meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 48:894–908, 2009.

Cortese S, Konofal E, Yateman N, Mouren MC, Lecendreux M: Sleep and alertness in children with attention-deficit/hyperactivity disorder: A systematic review of the literature. Sleep 29:504–511, 2006.

De Crescenzo F, Armando M, Mazzone L, Ciliberto M, Sciannamea M, Figueroa C, Janiri L, Quested D, Vicari S: The use of actigraphy in the monitoring of methylphenidate versus placebo in ADHD: A meta-analysis. Atten Defic Hyperact Disord 6:49–58, 2014.

Faraone SV, Glatt SJ, Bukstein OG, Lopez FA, Arnold LE, Findling RL: Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. J Atten Disord 12:308–315, 2009.

Giblin JM, Strobel AL: Effect of lisdexamfetamine dimesylate on sleep in children with ADHD. J Atten Disord 15:491–498, 2011.

Gruber R, Fontil L, Bergmame L, Wiebe ST, Amsel R, Frenette S, Carrier J: Contributions of circadian tendencies and behavioral problems to sleep onset problems of children with ADHD. BMC Psychiatry 12:212, 2012.

Hiscock H, Sciberras E, Mensah F, Gerner B, Efron D, Khano S, Oberklaid F: Impact of a behavioural sleep intervention on symptoms and sleep in children with attention deficit hyperactivity disorder, and parental mental health: Randomised controlled trial. BMJ 350:h68, 2015.

Hvolby A: Associations of sleep disturbance with ADHD: Implications for treatment. Atten Defic Hyperact Disord 7:1–18, 2015.

Kent JD, Blader JC, Koplewicz HS, Abikoff H, Foley CA: Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorder. Pediatrics 96:320–325, 1995.

Kidwell KM, Van Dyk TR, Lundahl A, Nelson TD: Stimulant medications and sleep for youth with ADHD: A meta-analysis. Pediatrics 136:1144–1153, 2015.

Kim H-W, Yoon I-Y, Cho S-C, Kim B-N, Chung S, Lee H, Kim C-W, Park S-K, Yoo HJ: The effect of OROS methylphenidate on the sleep of children with attention-deficit/hyperactivity disorder. Int Clin Psychopharmacol 25:107–115, 2010.

Markovich AN, Gendron MA, Corkum PV: Validating the Children's Sleep Habits Questionnaire against polysomnography and actigraphy in school-aged children. Front Psychiatry 5:188, 2014.

Mayes SD, Calhoun SL, Bixler EO, Vgontzas AN, Mahr F, Hillwig-Garcia J, Elamir B, Edhere-Ekezie L, Parvin M: ADHD subtypes and comorbid anxiety, depression, and oppositional-defiant disorder: Differences in sleep problems. J Pediatr Psychol 34:328–337, 2009.

National Sleep Foundation: ADHD and sleep, 2015. Available at http://sleepfoundation.org/sleep-disorders-problems/adhd-and-sleep (Accessed June 22, 2015).

O'Brien LM, Ivanenko A, Crabtree VM, Holbrook CR, Bruner JL, Klaus CJ, Gozal D: The effect of stimulants on sleep characteristics in children with attention deficit/hyperactivity disorder. Sleep Med 4:309–316, 2003.

Owens JA: A clinical overview of sleep and attention-deficit/hyperactivity disorder in children and adolescents. J Can Acad Child Adolesc Psychiatry 18:92–102, 2009.

Owens JA, Maxim R, Nobile C, McGuinn M, Msall M: Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 154:549–555, 2000a.

Owens JA, Spirito A, McGuinn M: The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep 23:1043–1051, 2000b.

Owens JA, Spirito A, McGuinn M, Nobile C: Sleep habits and sleep disturbance in elementary school-aged children. J Dev Behav Pediatr 21:27–36, 2000c.

Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D: Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep 29:1573–1585, 2006.

Santisteban JA, Stein MA, Bergmame L, Gruber R: Effect of extended-release dexmethylphenidate and mixed amphetamine salts on sleep: A double-blind, randomized, crossover study in youth with attention-deficit hyperactivity disorder. CNS Drugs 28:825–833, 2014.

Stein MA, Weiss M, Hlavaty L: ADHD treatments, sleep, and sleep problems: Complex associations. Neurotherapeutics 9:509–517, 2012.

Sung V, Hiscock H, Sciberras E, Efron D: Sleep problems in children with attention-deficit/hyperactivity disorder: Prevalence and the effect on the child and family. Arch Pediatr Adolesc Med 162:336–342, 2008.

Walters AS, Silvestri R, Zucconi M, Chandrashekariah R, Konofal E: Review of the possible relationship and hypothetical links between attention deficit hyperactivity disorder (ADHD) and the simple sleep related movement disorders, parasomnias, hypersomnias, and circadian rhythm disorders. J Clin Sleep Med 4:591–600, 2008.

Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD: Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. J Am Acad Child Adolesc Psychiatry 45:512–519, 2006.

Wigal SB, Greenhill LL, Nordbrock E, Connor DF, Kollins SH, Adjei A, Childress A, Stehli A, Kupper RJ: A randomized placebo-controlled double-blind study evaluating the time course of response to methylphenidate hydrochloride extended-release capsules in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 24:562–569, 2014.

Wigal SB, Nordbrock E, Adjei A, Childress A, Kupper RJ, Greenhill L: Efficacy of methylphenidate hydrochloride extended-release capsules (Aptensio XR™) in children and adolescents with attention-deficit/hyperactivity disorder: A phase III, randomized, double-blind study. CNS Drugs 29:331–340, 2015.

Wigal SB, Wigal TL: The laboratory school protocol: Its origin, use, and new applications. J Atten Disord 10:92–111, 2006.

Wiggs L, Montgomery P, Stores G: Actigraphic and parent reports of sleep patterns and sleep disorders in children with subtypes of attention-deficit hyperactivity disorder. Sleep 28:1437–1445, 2005.

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