Poster 52

Serdexmethylphenidate/Dexmethylphenidate Effects on Sleep in Children With Attention-Deficit Hyperactivity Disorder

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INTRODUCTION

- Sleep-related problems are common in children with attention-deficit hyperactivity disorder (ADHD).[1]
- Stimulant medications for ADHD can potentially affect sleep.[2]
- Serdexmethylphenidate/dexmethylphenidate (SDX/d-MPH; Azstarys®) is a once-daily treatment approved for patients aged ≥6 years with ADHD.[3]
- SDX is a novel prodrug of d-MPH.
- SDX/d-MPH contains a fixed molar ratio of 70% SDX and 30% d-MPH.[3]
- Efficacy and safety of SDX/d-MPH were reported from a 1-month pivotal double-blind, laboratory classroom study of children aged 6-12 years with ADHD.[4]

OBJECTIVE

- The objective was to assess sleep behavior with SDX/d-MPH treatment for up to 1 year in children with ADHD.

METHODS

Study Design

- This was a 1-year, dose-optimized, open-label safety study with SDX/d-MPH administered orally in children aged 6-12 years with ADHD (NCT03460652).
- The study consisted of a 30-day screening phase, a 3-week dose-optimization (DO) phase (for new subjects), a 360-day treatment phase, and a follow-up visit.
- The study involved new subjects and subjects from the double-blind study who were rolled over into the current trial within 45 days of their last dose of SDX/d-MPH from the double-blind study (rollover subjects).
- For new subjects only, during the DO phase, subjects started treatment with 39.2/7.8 mg SDX/d-MPH daily for 7 days. Dose adjustments, if needed, were performed at approximately weekly intervals. The dose at the end of the third week was assigned as the optimized dose consisting of 26.1/5.2 mg, 39.2/7.8 mg, or 52.3/10.4 mg SDX/d-MPH daily, which are 20-, 30-, and 40-mg molar equivalent doses of total d-MPH HCl.
- For new subjects, the starting dose during the treatment phase was the optimized SDX/d-MPH dose at the end of the DO phase. For rollover subjects, the starting dose in the treatment phase was the same as their optimized dose from the previous study.
- The primary end point was safety and tolerability of SDX/d-MPH. Sleep behavior based on the Children's Sleep Habits Questionnaire (CSHQ)[5] assessments was a secondary end point.

Assessments

- CSHQ assesses 8 sleep domains: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness.[5]
  - All CSHQ assessments and baseline data were analyzed using the treatment phase safety population, which included subjects who received ≥1 dose of SDX/d-MPH in the treatment phase and had ≥1 postdose safety assessment in the treatment phase.
  - Of a total CSHQ score of 99, the clinical cutoff indicating the presence of sleep disorders is a score ≥41.[5]
  - A reduction in CSHQ scores indicates improvement in sleep.

Statistical Analysis

- A mixed-effect model for repeated measures was used to determine change from baseline to each postbaseline study visit for each CSHQ sleep score domain.
- The Bonferroni method was used to determine statistical significance.

RESULTS

Subjects

- Of 282 subjects enrolled (212 new and 70 rollover), 238 were included in the sleep analysis.
- The subjects' demographics and baseline characteristics are shown in **Table 1**.
  - Most subjects reported sleep disturbances. At baseline, the mean (SD) CSHQ score was 53.4 (5.9).

Table 1. Subject demographics and baseline characteristics.

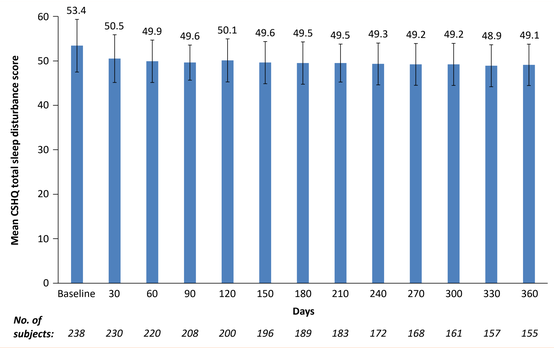
Parameter	Subjects (N = 238)
Age, y	9.1 (1.87)
Sex, n (%)	
Male	145 (60.9)
Female	93 (39.1)
Ethnicity, n (%)	
Hispanic or Latino	45 (18.9)
Not Hispanic or Latino	193 (81.1)
Race, n (%)	
White	113 (47.5)
Black/African American	111 (46.6)
Multiracial	9 (3.8)
Asian	2 (0.8)
Other	2 (0.8)
American Indian/Alaska Native	1 (0.4)
Weight, kg	38.6 (13.9)
Height, cm	139.6 (11.9)
Body mass index, kg/m²	19.3 (4.6)
CSHQ total score	53.4 (5.9)
ADHD-RS-5, overall score	41.5 (7.7)
CGI-S score	4.7 (0.7)

Values shown are mean (SD) unless otherwise noted.
ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale-5; CGI-S, Clinical Global Impressions–Severity; CSHQ, Children's Sleep Habits Questionnaire.

Sleep Assessment

- After 1 month of treatment, the total mean (SD) CSHQ sleep disturbance score significantly decreased to 50.5 (5.4; **Figure 1;** least-squares mean change from baseline −2.9 [95% CI, −3.5 to −2.4; $P < .0001$]) and remained in the 48.9 to 50.1 range for up to 12 months, indicating sustained overall sleep improvement.
- Although total sleep disturbance scores were almost all ≥41 (99.2% at baseline and 100% at 12 months), there was a shift towards a higher number of subjects with lower total sleep disturbance scores at 12 months versus at baseline (**Figure 2**).
- Mean sleep-score improvements from baseline to 12 months were statistically significant ($P < .0001$) for 6 of 8 sleep domains. These included bedtime resistance, sleep onset, sleep anxiety, night wakings, parasomnias, and daytime sleepiness (**Table 2**).
  - Parasomnias and daytime sleepiness sleep domains had the greatest mean improvement from baseline to 12 months.
  - Sleep onset and sleep duration scores increased from baseline to 12 months.
  - There was no significant worsening from baseline in sleep duration and sleep-disordered breathing domains.

Figure 1. Mean CSHQ total sleep disturbance score by study visits for up to 12 months.



Bars are standard deviations.
CSHQ, Children's Sleep Habits Questionnaire.

Table 2. Mean and change from baseline in CSHQ sleep domain scores.

Sleep domain	Baseline Mean (SD)	SDX/d-MPH treatment at 12 months Mean (SD) LS mean change from baseline (95% CI), *P* value
Bedtime resistance	10.8 (1.7)	10.1 (1.1) −0.7 (−0.9, −0.6), $P < .0001$
Sleep onset	2.2 (0.8)	2.6 (0.7) 0.4 (0.3, 0.5), $P < .0001$
Sleep duration	6.6 (1.1)	6.8 (0.7) 0.2 (0.04, 0.28), $P = .0091$
Sleep anxiety	5.5 (2.0)	4.6 (1.5) −0.9 (−1.0, −0.7), $P < .0001$
Night wakings	4.1 (1.3)	3.6 (1.0) −0.5 (−0.6, −0.4), $P < .0001$
Parasomnias	8.9 (1.9)	7.9 (1.4) −1.1 (−1.3, −0.9), $P < .0001$
Sleep-disordered breathing	3.4 (0.9)	3.2 (0.6) −0.1 (−0.9, −0.02), $P = .0111$
Daytime sleepiness	14.6 (3.02)	12.6 (2.8) −2.0 (−2.4, −1.7), $P < .0001$

LS, least-squares; SDX/d-MPH, serdexmethylphenidate/dexmethylphenidate.

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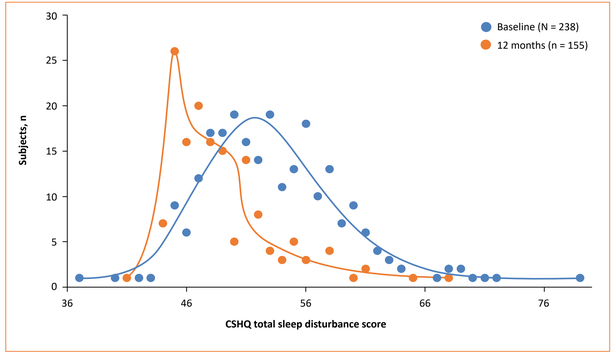
Figure 2. Frequency distribution of CSHQ total sleep disturbance score at baseline and 12 months.



Bars are standard errors.
CSHQ, Children's Sleep Habits Questionnaire..

CONCLUSIONS

- In this study of children taking SDX/d-MPH for ADHD, statistically significant improvements in most CSHQ sleep domains were observed after 1 month and lasted for up to 12 months of treatment.
  - Importantly, the use of SDX/d-MPH did not worsen sleep problems.

DISCLOSURES

GWM: consultant fees or honoraria from AbbVie, Acadia, Alkermes, Avanir, Axsome, Boehringer, Eisai, Emalex, Ironshore, Intra-Cellular, Janssen, Lundbeck, Medgenics, Neos, Neurocrine, NLS-1 Pharma AG, Otsuka, Redax, Rhodes, Roche, Sage, Shire, Sunovion, Supernus, Takeda, Teva, and Tris Pharma. **ACC:** consultant for Arbor, Ironshore, Neos Therapeutics, Neurovance, Purdue, Rhodes, Sunovion, Tris Pharma, KemPharm, Supernus, Jazz, Corium, and Lumos; speakers' bureau for Takeda (Shire), Arbor, Ironshore, Neos Therapeutics, Tris Pharma, and Supernus; research support from Allergan, Takeda (Shire), Emalex, Pearson, Akili, Arbor, Ironshore, Aevi Genomic Medicine, Neos Therapeutics, Neurovance, Otsuka, Purdue, Adlon, Rhodes, Sunovion, Tris Pharma, KemPharm, Supernus, US Food and Drug Administration, and Servier; writing support from Takeda (Shire), Arbor, Ironshore, Neos Therapeutics, Purdue, Rhodes, Sunovion, and Tris Pharma; and advisory board for Takeda (Shire), Akili, Arbor, Cingulate, Ironshore, Neos Therapeutics, Neurovance, Otsuka, Purdue, Adlon, Rhodes, Sunovion, Tris Pharma, Supernus, NLS Pharma, and Corium. **AJC:** consultant for Adlon Therapeutics, Aevi Genomics, Akili Interactive, Allergan/AbbVie, Arbor Pharmaceuticals, Attentive, Corium, Ironshore, Otsuka, Purdue Canada, Reviva Pharmaceuticals, Sunovion, Supernus, Shire/Takeda, and Tris Pharma; speakers' bureau for Arbor Pharmaceuticals, Allergan/AbbVie, Corium, Ironshore, Otsuka, Sunovion, Supernus, Shire/Takeda, and Tris Pharma; and research support from Aevi Genomics, Akili Interactive, Allergan/AbbVie, Arbor Pharmaceuticals, KemPharm, Ironshore, Otsuka, Purdue Canada, Rhodes, Shire, Sunovion, Supernus, and Takeda. **JE** and **MC:** employees of Corium, Inc.

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