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Analysis of Daily Sleep Diary Measures From Multilayer Extended-Release Methylphenidate (PRC-063) Studies in Children and Adults With ADHD

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Abstract

Objective: To compare the effect of a once-daily extended-release methylphenidate formulation (PRC-063) versus placebo on sleep, measured via daily electronic diary in two clinical trials in pediatric (6–12 years) and adult (≥18 years) patients with attention deficit hyperactivity disorder (ADHD). **Method:** A diary was completed by adult patients or parents/caregivers of pediatric patients during two randomized, double-blind, placebo-controlled laboratory classroom studies. Following dose optimization of PRC-063, patients were randomized to 1 week of double-blind treatment with PRC-063 or placebo before attending a full-day laboratory classroom session. **Results:** In the studies, 148 pediatric patients and 239 adult patients were randomized to either PRC-063 or placebo. When compared with the diaries of placebo patients, the sleep diaries in both pediatric and adult patients showed no statistical difference in total sleep time, efficiency, or latency. **Conclusion:** PRC-063 did not impact subjective measures of sleep versus placebo in pediatric and adult patients with ADHD. *(J. of Att. Dis. 2022; 26(14) 1870-1881)*

Keywords

adult ADHD, electronic diary, methylphenidate, methylphenidate, sleep, extended-release stimulant

Introduction

Central nervous system (CNS) stimulants are recognized first-line treatments for attention deficit hyperactivity disorder (ADHD) in pediatric patients and adults, along with other non-pharmacologic treatment interventions (NICE guidelines, 2018; Wolraich et al., 2019). Methylphenidate has a robust evidence base for the treatment of ADHD across the life span and is one of the most widely prescribed medications for the management of ADHD symptoms (Fallu et al., 2016; Huss et al., 2017, 2014; Storebø et al., 2018). Although extended-release preparations of methylphenidate are available, caregivers of pediatric patients and adolescents with ADHD commonly report that the effectiveness of these medications generally wanes beyond school hours (Sikirica et al., 2015), leading to a desire to further extend the therapeutic duration of effect. Guidelines recommend treatment in settings where impairment exists and for many patients that can cross multiple domains, thus necessitating the need for agents with extended therapeutic durations (Canadian ADHD Resource Alliance, 2020). In adults, ADHD can cause a range of impairments from morning to evening, creating a need for a once-daily medication with a rapid onset of action (≤1 hour) and a long duration of effect (Bjerrum et al., 2017; Spencer et al., 2008; T. Wigal et al., 2018).

The benefits of prolonging the duration of action of extended-release methylphenidate must be weighed against possible adverse effects. The impact of CNS stimulants on

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sleep has been an area of focus, with greater concern for agents with longer therapeutic duration (Corkum et al., 2020; Kidwell et al., 2015). Determining the impact of CNS stimulants on sleep is complicated by the association of untreated ADHD with sleep disturbances in both pediatric and adult patients (Bjorvatn et al., 2017; Ruiz-Herrera et al., 2020; Virring et al., 2017). In placebo-controlled clinical trials of CNS stimulants for the treatment of ADHD, commonly reported adverse effects include delayed sleep onset, insomnia, and increased wakefulness (Weyandt et al., 2014). As sleep disturbances related to ADHD medication are most common in the first few weeks of treatment, results from short-term efficacy trials can provide meaningful guidance to clinicians (Cortese 2020; Kidwell et al., 2015; Storebø et al., 2018). Interestingly, some research employing sleep specific outcome measures has demonstrated little negative impact of CNS stimulants on sleep or even improvement in certain sleep parameters in some patients with ADHD (Giblin et al., 2011; Kooij et al., 2001; Owens et al., 2016; Sobanski et al., 2008; Surman et al., 2011; Weiss, Surman, Khullar, He, et al., 2021; Weiss, Surman, Khullar, Owens, et al., 2021). Meta-analyses have identified CNS stimulant formulation as one source of the variability in sleep outcomes (Faraone et al., 2019; Kidwell et al., 2015).

PRC-063 is an extended-release formulation of methylphenidate intended for morning administration and designed to provide rapid onset and an extended duration of action (Katzman et al., 2020). PRC-063 is formulated with a multilayer-release bead technology yielding a biphasic pharmacokinetic profile with an initial time to maximum plasma concentration (T_{max}) in adults at 1.5 hours postdose and a second T_{max} at 12 hours postdose, about 4 to 6 hours later than most long-acting methylphenidate formulations. Studies demonstrated that the pharmacokinetic profile of PRC-063 in pediatric patients aged 6 to 11 years is comparable to that of adults, with the median first peak plasma concentration occurring at about 2 hours (range, 1–4 hours) and the second peak at about 10 hours (range, 8–14 hours; Adhansia XR, 2021).

Two similarly designed, randomized, double-blind, placebo-controlled, parallel group laboratory classroom clinical trials were conducted to evaluate the clinical efficacy and safety of PRC-063 compared with placebo. One clinical trial was conducted in pediatric patients aged 6 to 12 years (Childress et al., 2020; NCT03172481), and one trial was conducted in adults aged 18 to 55 years (Childress et al., 2021; NCT03618030). The primary results demonstrated that pediatric patients who received PRC-063 had a significant improvement in attention compared with those who received placebo, with an onset of effect at 1 hour and a duration of clinical effect lasting 13 hours, the last time point measured. In the adult study, patients who received PRC-063 had a significant improvement in attention compared with those who received placebo, with an onset of effect at 1 hour and a duration of clinical effect lasting up to and including 16 hours, the last time point measured. These studies did not gather structured ratings of sleep outcomes, but a daily sleep diary was completed by parent/guardians or patients. In two previous placebo-controlled, double-blind studies, evaluating PRC-063 for the treatment of ADHD over 4 weeks, self-rated sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI; Weiss, Surman, Khullar, He, et al., 2021; Weiss, Surman, Khullar, Owens, et al., 2021). In both age groups, PSQI ratings did not differ between active treatment and placebo.

Sleep diaries are the standard approach for collecting self-reported data on sleep duration and quality, and may gather more precise information than less frequently administered sleep questionnaires (Mallinson et al., 2019). Therefore, we conducted a post hoc analysis using daily sleep diary data from the pediatric and adult laboratory classroom studies, described above, to compare the effect of PRC-063 and placebo on subjective sleep measures (Purdue Pharma, 2021).

Methods

Study Design, Treatment, and Participants

This was a post hoc analysis of daily sleep diary data that were collected as part of two phase 3, randomized, double-blind, placebo-controlled parallel-group studies that evaluated the safety and efficacy of PRC-063, the first in pediatric patients (6–12 years of age) with ADHD and the second in adult patients (≥18 years of age) with ADHD. Details of the two studies have been published previously and can be found at ClinicalTrials.gov Identifiers NCT03172481 (Childress et al., 2020) and NCT03618030 (Childress et al., 2021). The pediatric study was conducted at six sites in the United States (US) from May 2017 to August 2017 and the adult study was conducted at eight sites in the US from August 2018 to July 2019.

The pediatric and adult studies followed the same study design, unless otherwise noted. Briefly, these studies comprised four periods: screening (up to 28 days), 3-day washout, open-label dose optimization (up to 6 weeks in pediatric patients and 7 weeks in adult patients), and a 7-day double-blind, randomized, placebo-controlled period, which is the focus of this post hoc analysis. During the 7-day double-blind period, patients were randomized to receive either PRC-063 (dose established during the optimization period) or placebo.

In both studies, patients were considered dose optimized once a 30% reduction in ADHD symptoms from baseline was achieved, accompanied by a score of 1 or 2 on the clinician-administered Clinical Global Impressions Improvement (CGI-I) scale and acceptable tolerability to PRC-063. Pediatric patients were optimized on one of the following

once-daily dosages of PRC-063: 25, 35, 45, 55, 70, or 85 mg. Adult patients were optimized on one of the following once-daily dosages of PRC-063: 25, 35, 45, 55, 70, 85, or 100 mg.

Sleep Diaries

Sleep diary methodology is an accepted standard for assessing subjective sleep measures that enables collection of details in real time versus recalled information about daily sleep duration and timing over a specified period (Carney et al., 2012; Ibáñez et al., 2018). The sleep diary items for these studies were adapted from the National Sleep Foundation's Sleep Diary (National Sleep Foundation's Sleep Diary website: https://www.thensf.org/nsf-sleep-diary/) and published recommendations (Carney et al., 2012). Pediatric patients' parents/caregivers were instructed on how to complete a daily dosing diary to record the date and time of dosing, as well as a 20-question daily sleep diary to record information including bedtime, number of hours of sleep, and sleep quality (Adapted from https://www.thensf.org/wp-content/uploads/2021/02/NSF-Sleep-Diary-Rev-2-2021.pdf). Adult patients were provided with and instructed to complete a similar 27-question daily sleep diary (Adapted from https://www.thensf.org/wp-content/uploads/2021/02/NSF-Sleep-Diary-Rev-2-2021.pdf). The diary items included general questions (e.g., amount of time slept) answered by all patients and conditional questions. In the pediatric study, the conditional question was "if child woke up, the number of minutes the child was awake." In the adult study, the conditional questions were "if woke up, number of times awake during the night" and "number of minutes awake."

Sleep difficulty was rated as falling asleep "easily," "after some time," or "with difficulty." Total sleep time (TST) was recorded based on "amount of time slept last night (hours)." Time in bed (TIB) was calculated based on "time out of bed" and "bedtime last night." Sleep efficiency was calculated as the ratio of TST to TIB expressed as a percentage. The number of minutes awake during the night was recorded, with an assignment of 0 for nights with no report of waking up during the night. Mood upon awakening was described as "rested," "somewhat rested," or "tired." Additionally, adult patients rated sleep onset latency based on "time spent getting to sleep." Sleep latency was not assessed in pediatric patients because of the questionable validity of parental estimates of this information. Insomnia diagnosis or symptoms reported by patients at baseline was recorded in medical history and as an adverse medication effect during treatment.

Statistical Analysis

Descriptive analysis was used for demographic and clinical characteristics. Continuous variables were summarized using descriptive statistics (i.e., *n*, mean, and standard deviation [*SD*]). Categorical variables were summarized by number of participants and percent distribution by category. The two-sided t-test was used to compare the mean of continuous study outcomes for PRC-063 versus placebo. Two-sided Pearson's chi-square test (or Fisher's exact test in case of low sample sizes) was performed to compare the distribution between PRC-063 and placebo groups for categorical outcomes. Summary statistics were calculated using SAS v9.4 (SAS Institute Inc., NC, USA).

The analysis was also conducted on the study outcomes stratified by the PRC-063 dose group (lower dose [25, 35, 45, and 55 mg for adult patients, 25, 35, and 45 mg for pediatric patients], upper dose [70, 85, and 100 mg for adult patients, 55, 70, and 85 mg for pediatric patients]), placebo, insomnia status at baseline, age, and ADHD severity. Multivariable analysis, using generalized linear models (PROC GLIMMIX in SAS), was used for TST and sleep efficiency scores, adjusting for the following covariates: age group, gender, race, ethnicity, body mass index (BMI) at baseline, ADHD presentation, baseline total score for ADHD-RS-5, and presence of insomnia at baseline. Further multivariable analysis was performed to assess sleep latency with the same covariates as listed above.

Results

Baseline Demographics

In the pediatric study, a total of 148 pediatric patients were randomized to either PRC-063 (75 patients) or placebo (73 patients). Baseline demographic and clinical characteristics for the pediatric study are summarized in Table 1 (Childress et al., 2020). The mean age of the patients was 9.4 years, 65% were male, most were White (55%) or Black/African American (39%), and most (85%) had the combined ADHD presentation. At baseline, the PRC-063 and placebo groups had similar and statistically non-significant ADHD-RS-5 total scores, with low numbers of patients in either group reporting a medical history of insomnia. Most pediatric patients ($n = 95$, 64%) had received prior treatment with psychostimulants for ADHD. With the exception of one pediatric patient who received diphenhydramine for an unspecified diagnosis (sleep vs. allergy), no pediatric patients received concomitant medications for sleep.

Adherence to diary use was considered to be high. During the double-blind period, 89% to 95% of pediatric patients had at least one entry per week for general questions (https://www.thensf.org/wp-content/uploads/2021/02/NSF-Sleep-Diary-Rev-2-2021.pdf) and the mean number of days per week with data entry ranged from 5.4 to 5.6. All conditional questions were answered for those patients who fulfilled the criteria (i.e., woke up at least once during the night).

In the adult study, a total of 239 adult patients were randomized to either PRC-063 (121 patients) or placebo (118

Table 1. Baseline Demographics and Clinical Characteristics: PRC-063 Pediatric Study[a] (*N* = 148).

Baseline demographics and clinical characteristics	Placebo (*n* = 73)	PRC-063 (*n* = 75)
Age (years), *M* (*SD*)	9.4 (1.83)	9.4 (1.92)
Age group, *n* (%)		
Age 6	4 (5.5)	7 (9.3)
Age 7	8 (11.0)	7 (9.3)
Age 8	16 (21.9)	11 (14.7)
Age 9	10 (13.7)	15 (20.0)
Age 10	13 (17.8)	10 (13.3)
Age 11	9 (12.3)	11 (14.7)
Age 12	13 (17.8)	14 (18.7)
Gender, *n* (%)		
Female	24 (32.9)	28 (37.3)
Male	49 (67.1)	47 (62.7)
Race, *n* (%)		
White	34 (46.6)	48 (64.0)
Black/African American	33 (45.2)	25 (33.3)
Asian	1 (1.4)	0 (0.0)
Other	5 (6.8)	2 (2.7)
Ethnicity, *n* (%)		
Hispanic or Latino	21 (28.8)	21 (28.0)
Not Hispanic or Latino	52 (71.2)	54 (72.0)
ADHD presentation, *n* (%)		
Combined	64 (87.7)	62 (82.7)
Inattentive	9 (12.3)	13 (17.3)
ADHD-RS-5 total score		
Mean (*SD*)	42.8 (7.37)	42.9 (7.09)
ADHD-RS-5 total score group, *n* (%)		
Moderate (19–36)	11 (15.1)	14 (18.7)
Severe (37–54)	62 (84.9)	61 (81.3)
Medical history of insomnia at baseline, *n* (%)		
Yes	6 (8.2)	2 (2.7)
No	67 (91.8)	73 (97.3)
Prior stimulant treatment, *n* (%)		
Yes	52 (71.2)	43 (57.3)
No	21 (28.8)	32 (42.7)

Note. ADHD-RS-5 = ADHD Rating Scale 5; *SD* = standard deviation.
[a]Study groups were statistically similar ($p > .05$) in all characteristics.

patients). Baseline demographic and clinical characteristics for the adult study are summarized in Table 2 (Childress et al., 2021). The mean age of the patients was 33.5 years, 54% were female, most were White (75%), and most had the combined ADHD presentation (84%). The PRC-063 and placebo groups had comparable ADHD-RS-IV total scores at baseline. Most patients (*n* = 115 [95%] PRC-063 group, *n* = 105 [89%] placebo group) reported no baseline medical history of insomnia. The number of patients with baseline insomnia who received placebo was numerically higher, but this difference was not statistically significant. Most adult patients (*n* = 172, 72%) had not received prior treatment with psychostimulants for ADHD, and no patients received concomitant sleep medications.

As with the pediatric data, the adherence to diary use was considered to be high. During the double-blind period, 78% to 86% of adult patients had at least one entry per week for general questions and the mean number of days per week with data entry ranged from 4.6 to 5.0. All conditional questions, for patients who fulfilled the criteria for conditional questions (i.e., woke up during the night), were answered.

In the pediatric study, subjective sleep measures were similar in patients receiving PRC-063 and those receiving placebo (Figure 1 and Supplemental Appendix 1). Sleep difficulty, TST, TIB, sleep efficiency, number of times the patient woke up at night, amount of time awake at night, and mood on awakening were similar in pediatric patients

Table 2. Baseline Demographics and Clinical Characteristics: PRC-063 Adult Study[a] (*N* = 239).

Baseline demographics and clinical characteristics	Placebo (*n* = 118)	PRC-063 (*n* = 121)
Age (years), *M* (*SD*)	32.8 (10.95)	34.1 (10.76)
Age group, *n* (%)		
18–19	11 (9.3)	7 (5.8)
20–29	40 (33.9)	39 (32.2)
30–39	36 (30.5)	43 (35.5)
40–49	20 (16.9)	18 (14.9)
50–60	11 (9.3)	14 (11.6)
Gender, *n* (%)		
Female	64 (54.2)	66 (54.5)
Male	54 (45.8)	55 (45.5)
Race, *n* (%)		
White	90 (76.3)	90 (74.4)
Black/African American	21 (17.8)	24 (19.8)
Asian	2 (1.7)	3 (2.5)
Other	4 (3.4)	4 (3.3)
Unknown	1 (0.8)	0 (0.0)
Ethnicity, *n* (%)		
Hispanic or Latino	24 (20.3)	18 (14.9)
Not Hispanic or Latino	93 (78.8)	102 (84.3)
Not reported	1 (0.8)	1 (0.8)
ADHD presentation, *n* (%)		
Combined	102 (86.4)	98 (81.0)
Hyperactive/impulsive	1 (0.8)	1 (0.8)
Inattentive	15 (12.7)	22 (18.2)
ADHD-RS-IV total score		
Mean (SD)	39.1 (6.92)	39.0 (6.55)
Minimum-maximum	28.0 - 54.0	28.0 - 53.0
ADHD-RS-IV total score group, *n* (%)		
Moderate (19–36)	48 (40.7)	44 (36.4)
Severe (37–54)	70 (59.3)	77 (63.6)
Medical history of insomnia at baseline, *n* (%)		
Yes	13 (11.0)	6 (5.0)
No	105 (89.0)	115 (95.0)
Prior stimulant treatment, *n* (%)		
Yes	30 (25.4)	37 (30.6)
No	88 (74.6)	84 (69.4)

Note. ADHD-RS-IV = ADHD Rating Scale IV; *SD* = standard deviation.
[a]Study groups were statistically similar ($p > .05$) in all characteristics.

receiving PRC-063 or placebo, and all assessments were not statistically significant (Supplemental Appendix 2). A sensitivity analysis stratifying patients by those receiving lower doses (25, 35, and 45 mg) and upper doses (55, 70, and 85 mg) also showed no statistically significant difference between either the lower or upper doses of PRC-063 compared with placebo (Supplemental Appendix 3). Multivariable analysis, controlling for age group, gender, race, ethnicity, ADHD presentation, baseline ADHD-RS-5 total score severity group, BMI, and baseline insomnia, showed no statistically significant difference between patients receiving placebo or PRC-063 with regard to TST or sleep efficiency for the pediatric study (Table 3). A stratification analysis was performed evaluating sleep diary scores in patients with and without prior treatment with stimulants, and there was no statistically significant difference between these groups.

In the adult study, subjective sleep measures were similar in patients receiving PRC-063 and those receiving placebo (Figure 2 and Supplemental Appendix 4). Sleep difficulty, TST, TIB, sleep efficiency, sleep onset latency, and mood on awakening among all patients were similar in patients receiving PRC-063 or placebo. Among patients who woke up during the night, the number of times awake

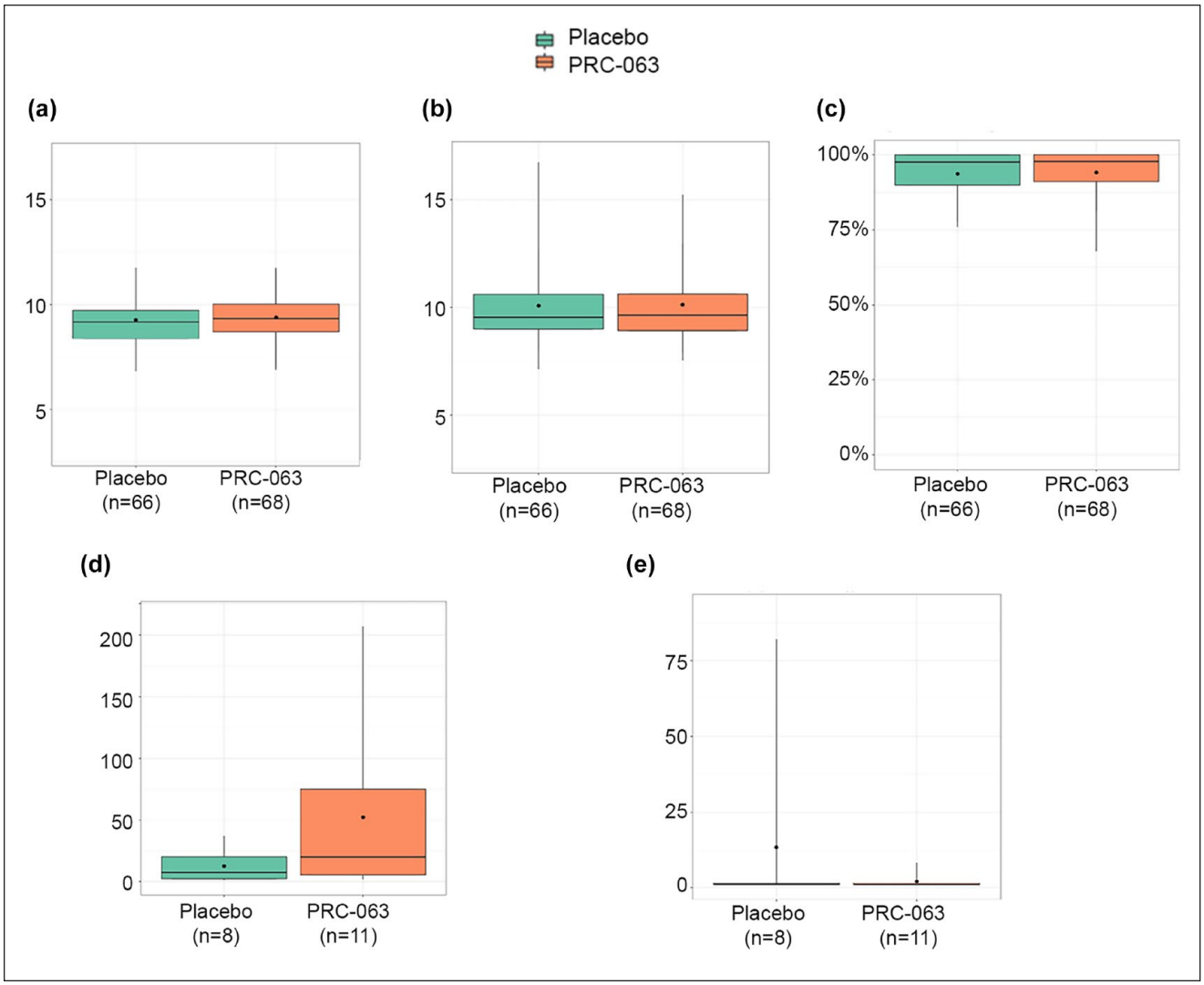

Figure 1. Sleep measures in pediatric patients: (a) total sleep time (hours), (b) time in bed (hours), (c) sleep efficiency, (d) number of minutes awake during the night (of patients who woke up), and (e) number of times patient woke up during the night (of patients who woke up). Note: The • in the box plot represents the mean, the shaded areas represent the middle 50 percentiles, and the error bars represent the 95% confidence intervals.

Table 3. Multivariable Analysis for Age Group, Gender, Race, Ethnicity, ADHD Presentation, Baseline ADHD-RS-5 Total Score, BMI, and Insomnia: PRC-063 Pediatric Study.

	Placebo ($n = 73$)	PRC-063 ($n = 75$)	p value
Total sleep time (TST), hours			
n	66	68	–
LS mean	9.15	9.28	0.5606
Sleep efficiency: TST/TIB × 100%			
n	66	68	–
LS mean	96.1	96.0	0.9506

Note. ADHD-RS-5 = ADHD Rating Scale 5; BMI = body mass index; TIB = time in bed; TST = total sleep time; LS mean = least-squares mean using generalized linear mixed models.

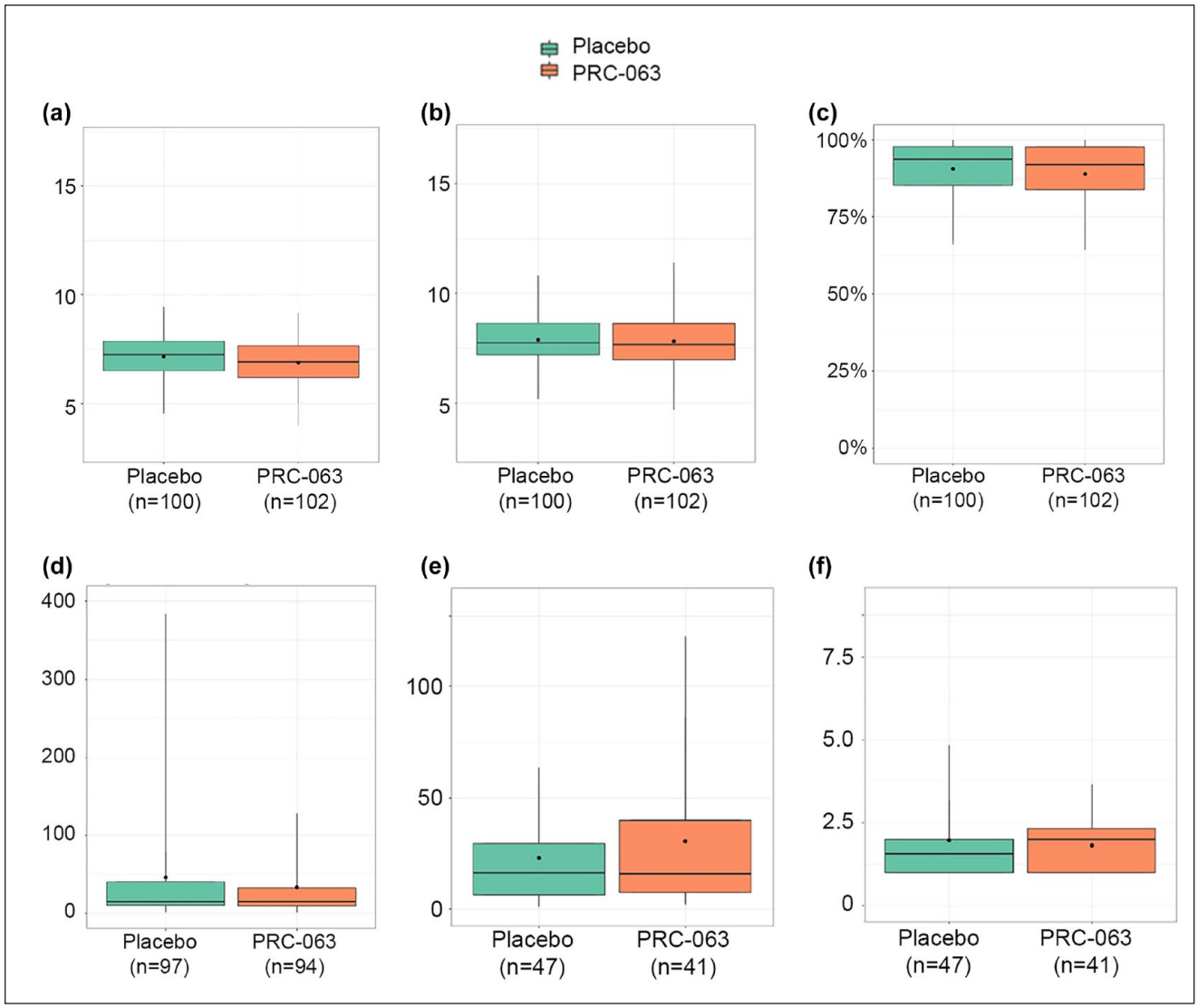

Figure 2. Sleep measures in adult patients: (a) total sleep time (hours), (b) time in bed (hours), (c) sleep efficiency, (d) sleep onset latency (minutes), (e) number of times minutes awake during the night (of patients who woke up), and (f) number of times awake during the night (of patients who woke up). Note: The • in the box plot represents the mean, the shaded areas represent the middle 50 percentiles, and the error bars represent the 95% confidence intervals.

and amount of time awake at night were similar in adult patients receiving PRC-063 or placebo. All assessments were not statistically different (Supplemental Appendix 5). A sensitivity analysis stratifying by lower doses (25, 35, 45, and 55 mg) and upper doses (70, 85, and 100 mg) showed no statistically significant difference between either the lower or upper doses of PRC-063 compared with placebo (Supplemental Appendix 6). Multivariable analysis, controlling for age group, gender, race, ethnicity, ADHD presentation, baseline total score for ADHD-RS-IV, BMI, and baseline insomnia, showed no statistically significant difference between placebo and PRC-063 with regard to TST, sleep efficiency, or sleep onset latency for the adult study (Table 4). A stratification analysis was performed evaluating sleep diary scores in patients with and without prior treatment with stimulants, and there was no statistically significant difference between these groups

Self-reported insomnia as a treatment emergent adverse event (AE) is defined as occurring during any period of the study after treatment initiation (i.e., open label or double blind). In the pediatric population, all insomnia AEs ($n=22$ across 19 different participants) were first reported during the open-label period of the study while receiving active PRC-063. The mean (standard deviation) duration of

Table 4. Multivariate Analysis Controlling for Age Group, Gender, Race, Ethnicity, ADHD Presentation, Baseline ADHD-RS-IV Total Score Group, Baseline BMI, and Baseline Insomnia: PRC-063 Adult Study.

	Placebo ($n = 118$)	PRC-063 ($n = 121$)	p value
Total sleep time (TST), hours			
n	100	102	–
LS mean	7.42	7.18	0.1961
Sleep efficiency: TST/TIB × 100%			
n	100	102	–
LS mean	91.8	90.1	0.3151
Sleep onset latency, minutes			
n	97	94	–
LS mean	36.1	28.9	0.4762

Note. ADHD-RS-IV = ADHD Rating Scale IV; BMI = body mass index; TIB = time in bed; TST = total sleep time; LS mean = least-squares mean using generalized linear mixed models.

insomnia events beginning in the open-label period was 20.7 days (18.0 days), and 8 (42%) pediatric participants reported insomnia AEs that persisted from the open label into the double-blind period. Of those eight pediatric participants, three were randomized to active PRC-063 and five to placebo. In pediatric patients who reported insomnia as an AE, subjective sleep measure results from sleep diaries were similar to those in patients with no insomnia AEs (data not shown).

For adults, there were 64 insomnia AEs across 58 participants. Insomnia was first reported by 54 adults during the open-label period and by 4 adults in the double-blind period. The mean (standard deviation) duration of insomnia events beginning in the open-label phase was 20.3 days (17.4 days), and 17 adults (29%) reported insomnia AEs that persisted from the open label into the double-blind period. Of those 17 adult participants, 8 were randomized to active PRC-063 and 9 to placebo. For the 4 patients with first reported insomnia AEs in the double-blind phase, 2 (50%) were assigned to active medication. Overall, adult patients who reported insomnia as an AE had similar subjective sleep measure results from their sleep diaries compared with those without insomnia AEs (data not shown).

Discussion

Sleep questionnaires are one of the most widely used techniques for evaluating sleep (Villalba-Heredia et al., 2021). The sleep diary is an accepted standard for self-reported subjective sleep measurement. It collects detailed real-time versus recalled information on daily sleep duration and timing that is not possible when documented at weekly or monthly visits during a clinical study (Carney et al., 2012). Diaries have been shown to capture more-precise estimates of subjective sleep parameters than existing rating scales (Mallinson et al., 2019). While insomnia and sleep-related AEs are commonly reported with CNS stimulants, including PRC-063 (Adhansia XR, 2021), this analysis sought to go beyond reports of spontaneous AEs to better understand sleep outcomes when prospectively collected via a daily sleep diary in dose-optimized patients.

There were no significant differences in any sleep diary parameters between groups in either the pediatric or adult study. These included TST, sleep onset latency, and sleep efficiency. Balancing the beneficial effects of the prolonged duration of action of extended-release stimulants with the potential detrimental effects on sleep is a significant concern in the treatment of ADHD. The availability of a stimulant with a duration of effect that covers the normal wake periods, without meaningfully worsening sleep versus placebo, provides a palatable option for patients with a history of sleep disturbances who seek extended control of their ADHD symptoms across the day.

When participants assigned to PRC-063 reported insomnia as an AE, most reports occurred during the initial open-label period. There were no new reports of insomnia AEs in the double-blind period in pediatric patients. In both the pediatric and adult study, more patients who reported insomnia AEs that persisted into the double-blind period of the study were receiving placebo. The observation that persistence of insomnia AEs was at least as likely in those receiving placebo versus PRC-063 suggests that other factors may be associated with persistence of sleep-related AEs other than just the use of CNS stimulants. The changes in rates of self-reported insomnia AEs from the open label to the blinded phases could have also been influenced by the change in participant/parent awareness of medication status given the appreciable effects of placebo on sleep (Winkler et al., 2015, Zheng et al., 2020). The prominence of the effects of placebo on sleep emphasizes the value of structured measures, such as the sleep diaries used in the current study, over sole reliance on unstructured, spontaneous reports of sleep-related AEs.

The improved tolerability of CNS stimulants over time for sleep parameters has been reported elsewhere (Cortese 2020; Kidwell et al., 2015; Storebø et al., 2018). In this study, sleep could have been further enhanced by the individualization of PRC-063 dosage during the open-label phase. As with other methylphenidate formulations, treatment with PRC-063 should be initiated at a low dose and titrated upwards as needed (Adhansia XR, 2021). A gradual titration may be especially important for patients with a history of insomnia given the higher rate of sleep-related AEs early in treatment.

Notably, the frequency of insomnia reported as an AE in patients receiving PRC-063 was lower than in studies of other oral extended-release methylphenidate products with a similar study design (Childress et al., 2017; S. B. Wigal et al., 2013, 2014, 2017). Theoretically, the heightened focus on sleep, resulting from continuous and repeated prompts to report on their sleep in the daily sleep diary, should have led to increased reporting of AEs.

Sleep disturbances are intrinsic to ADHD for some patients. Published reports on the incidence of insomnia in pediatric and adult patients with ADHD are as high as 25% to 50% (Brevik et al., 2017; Wajszilber et al., 2018). Interestingly, some research suggests that CNS stimulants (especially long-acting preparations) have little impact on sleep or can actually improve certain sleep parameters in some patients with ADHD (Becker et al., 2016; Giblin et al., 2011; Kooij et al., 2001; Owens et al., 2016; Roth et al., 2009; Sobanski et al., 2008; Solleveld et al., 2020; Surman et al., 2011). Without inclusion of structured measures to characterize pretreatment sleep, improved sleep indices with treatment may be erroneously identified as adverse effects. Unfortunately, such measures were not part of these studies but should be considered in future trials of CNS stimulants or other agents that may impact sleep.

Limitations

The study populations largely excluded patients with psychiatric comorbidities, and thus these findings may not be representative of a larger population of pediatric and adult patients diagnosed with ADHD. Seasonal changes in sleep patterns have been described (Mattingly et al., 2021), and school schedules can impact sleep duration in children (Bowers et al., 2017). Both of the studies in this analysis were mostly conducted during the summer, and thus the results may be different in other seasons. However, both active and placebo treatment groups would likely have been affected similarly by seasonal impacts. The relatively short duration of this study prevents generalization of these results over prolonged/chronic treatment. However, sleep indices appear to improve with extended treatment (Kidwell et al., 2015), suggesting that the encouraging tolerability profile may persist over time. Additionally, the study relied on self-reported and parent-reported data, the latter of which may pose inherent challenges to accurately complete the sleep diary measurements. The sleep diary is a recognized means of assessing sleep quality for pediatric and adult patients (Carney et al., 2012) and polysomnography, while the gold standard for diagnosing sleep disorders, has not enhanced detection of stimulant-induced sleep changes (Corkum et al., 2020).

The sample size of this post hoc study was not large enough to assess the effect of individual PRC-063 doses. Also, since patients were randomized after dose optimization, patients receiving placebo could have had a residual effect of PRC-063 in the first 1 to 2 days of the double-blind periods of each study that could have affected the results. This effect was mitigated by calculating the mean during the 7-day double-blind period. Additional analyses of daily sleep outcomes during the double-blind period (e.g., examining sleep values at the start of the week and later in the week) showed no significant differences in any of the sleep measures at the start of the 7-day double-blind period compared with the end, suggesting no residual effects of PRC-063 (data not shown). Baseline reports of a medical history of insomnia in these studies are lower than expected with baseline sleep data for both adult and pediatric patients showing generally age-normative sleep patterns; therefore, it is unclear how PRC-063 would affect patients with preexisting insomnia.

Conclusion

Insomnia is a commonly reported adverse effect of treatment associated with CNS stimulants, including PRC-063. To determine the impact of PRC-063 on sleep, we evaluated sleep impacts using sleep diary methodology in pediatric and adult patients with ADHD. Post hoc group data indicate that dose-optimized PRC-063 does not preferentially impact patient-reported sleep measures compared with placebo in pediatric or adult patients. PRC-063 was similar to placebo in all collected measures, including TST, sleep efficiency, and sleep onset latency. Therefore, in patients with ADHD and a history of healthy sleep patterns, PRC-063 may be an option for providing extended therapeutic coverage that does not have clinically detrimental impacts on sleep.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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