



Effect of a Multi-Layer, Extended-Release Methylphenidate Formulation (PRC-063) on Sleep in Adults with ADHD: A Randomized, Double-Blind, Forced-Dose, Placebo-Controlled Trial Followed by a 6-month Open-Label Extension

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Abstract

Background The effects of stimulant treatment on sleep in adults with attention-deficit/hyperactivity disorder (ADHD) are complex and varied, with some individuals experiencing worsening of sleep but others experiencing improvement.

Methods Data from previously reported trials of the clinical efficacy and safety of the long-acting methylphenidate formulation PRC-063 (Adhansia XR[®] in the USA; Foquest[®] in Canada) in adults with ADHD were used to evaluate patient-reported sleep outcomes, as captured using the Pittsburgh Sleep Quality Index (PSQI) and adverse events of insomnia. The trials comprised 4 weeks of randomized, forced-dose PRC-063 treatment at a dose of 0 (placebo), 25, 45, 70, or 100 mg/day followed by an optional 6 months of open-label PRC-063 treatment at an individually optimized dose of 25–100 mg/day.

Results At the end of double-blind treatment, PRC-063 (all doses combined; $N = 297$) showed no significant difference versus placebo ($N = 78$) in least squares mean change in global PSQI score from baseline (-0.7 vs. -1.3 ; $P = 0.0972$) or in scores for each of the seven subscales of the PSQI. For patients enrolled in the open-label extension ($N = 184$), mean \pm standard deviation global PSQI score improved from 7.8 ± 3.55 at the end of double-blind treatment to 5.8 ± 3.11 at 1 month and 5.4 ± 3.21 at 6 months ($P < 0.0001$). A greater proportion of patients were good sleepers (global PSQI score ≤ 5) at the end of the open-label extension (57.3%) than at baseline (20.9%) or at the end of double-blind treatment (26.0%). In a logistic regression analysis, baseline global PSQI score (odds ratio 1.491; $P < 0.0001$), but not randomized study treatment ($P = 0.1428$), was a significant predictor of poor sleep (global PSQI score > 5) at the end of double-blind treatment. Adverse event rates for insomnia (15.8 vs. 3.8%) and initial insomnia (6.1 vs. 1.3%) during double-blind treatment were higher for PRC-063 (all doses combined) than for placebo. Two patients receiving PRC-063 in the double-blind study and one patient in the open-label study were withdrawn because of insomnia adverse events.

Conclusions Our findings indicate that, on average, PRC-063 had no significant impact on overall sleep quality in adults with ADHD. Although insomnia was observed as an adverse event, when sleep was measured over time as an outcome in its own right for patients receiving dose-optimized PRC-063 open-label, more patients showed improvement in sleep than deterioration.

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1 Introduction

Adults with attention-deficit/hyperactivity disorder (ADHD) have been described as having multiple sleep disorders and deficits [1, 2]. Studies have consistently shown a higher cross-sectional prevalence of sleep problems in adults with ADHD versus those without ADHD [1, 3–13]. In a retrospective chart review study of 1828 nonmedicated patients

with ADHD, Fisher et al. [14] found that the increased prevalence of sleep problems in ADHD occurred across the lifespan, independent of sex, age, or ADHD subtype. These problems affected neuropsychological test performance and were more common in adults than in children or adolescents [14]. Brevik et al. [13] found that self-reported sleep complaints were more than twice as common in patients with ADHD than in population controls, with patients receiving stimulant treatment less likely to report such difficulties. A Canadian population study of 3908 women with ADHD reported an odds ratio of 5.08 for sleep problems, without controlling for medication use or comorbidity [15]. Several

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Key Points

In a 4-week, randomized, double-blind, placebo-controlled clinical trial and a 6-month open-label extension study of multilayer, extended-release methylphenidate (PRC-063) in adults with attention-deficit/hyperactivity disorder, participants assessed their own sleep using the Pittsburgh Sleep Quality Index.

More patients went from being poor sleepers to good sleepers than the other way around, and sleep for the group as a whole improved over time.

Insomnia is a common side effect of stimulant treatment, but group data indicated that an extended-release stimulant can actually improve sleep.

controlled studies using objective measures found sleep abnormalities in adults with ADHD: two actigraphy studies showed problems with sleep quality and insomnia in patients who were methylphenidate naïve [4] or who were currently unmedicated [16], and two polysomnography studies showed increased nocturnal motor activity in patients who were not currently taking stimulants or other psychotropic medications [3, 7]. There is overwhelming evidence that adults with ADHD have an increased risk of sleep problems, even controlling for use of medication and comorbidity, suggesting that sleep deficits are intrinsic to ADHD.

Two longitudinal studies have looked at the persistence of sleep problems in children with ADHD into adulthood [17, 18]. In a twin cohort study, Gregory et al. [17] found that 8.1% of their sample had ADHD at age 18 years, but two-thirds of these patients had not had ADHD in childhood. Sleep difficulties were problematic in patients who had ADHD in adulthood, irrespective of whether it was a late-onset diagnosis or persistent from childhood, suggesting that it is the ADHD symptoms themselves, whenever they are present across the lifespan, that are associated with sleep problems. In a second study looking at outcomes in subjects followed prospectively from birth to age 38 years, childhood ADHD was not associated with increased risk of sleep difficulties in adulthood [18]. ADHD in childhood, in and of itself, does not predict that sleep problems will endure unless the ADHD itself is persistent.

Studies have also confirmed an increased risk of specific sleep disorders in patients with ADHD. These disorders include circadian rhythm sleep–wake disorders [19–21] and, in particular, delayed sleep–wake phase disorder and/or an evening circadian preference or “eveningness” [22], sleep-onset insomnia (also referred to as initial insomnia) [4, 7, 9, 11], sleep maintenance [9, 23], short sleep duration [24], and reduced total sleep duration [23]. Adults with ADHD

frequently complain of poor sleep quality [17] and excessive daytime sleepiness [25, 26], findings confirmed with the mean sleep latency test [27]. Lastly, adults with ADHD are at greater risk of periodic limb movement syndrome [28], restless legs syndrome [29, 30], increased nocturnal motor activity [16], and sleep-disordered breathing [31]. Confirmation of these findings through polysomnography has been inconsistent [3, 7, 31], with the exception of increased motor activity [16].

Sleep deficits in adults with ADHD may not be evident in a polysomnogram completed over 1 or 2 nights but, rather, emerge most clearly with any method or instrument of sleep assessments that monitors sleep over time, such as self-report scales, actigraphy, or sleep logs. Impaired sleep has been demonstrated to affect attention, executive function, family well-being, and quality of life [32, 33]. In a study of children and youth, both sleep and ADHD contributed independently to functional impairment, reinforcing the importance of assessment and treatment of sleep issues in patients with ADHD to achieve optimal outcomes [34].

Treatment options for ADHD include stimulants, such as methylphenidate and amphetamines, and nonstimulant medications such as atomoxetine, clonidine, and guanfacine [35]. Although stimulants are a mainstay of treatment for ADHD in adults, one commonly reported adverse event (AE) for stimulant treatment is insomnia, especially sleep-onset insomnia [36]. Clinical trials of mixed amphetamine salts in adults have reported a rate of insomnia of 41.7 versus 12.5% for placebo, and clinical trials of lisdexamfetamine have reported a rate of insomnia of 10–19 versus 4–5% for placebo—a threefold increase in risk [37, 38]. Clinical trials of methylphenidate products in adults have also reported insomnia or other sleep problems as an AE in up to 33% of patients [39, 40]. Moreover, a recent meta-analysis of placebo-controlled trials in children and adolescents with ADHD found that methylphenidate was associated with increased risks of various insomnia AEs, including sleep-onset insomnia [41].

A limitation of these results is that patient reports of insomnia from clinical studies are highly sensitive to rate of titration, dose, and time on drug. A very different picture emerges of the relationship between stimulant treatment and sleep when sleep is evaluated systematically as an outcome in its own right in all patients rather than in patients for whom it is reported as a problem, without controlling for baseline sleep difficulties.

On the other hand, contrary to published studies indicating that stimulants can be detrimental to sleep and the common perception that most or all patients who receive stimulants are likely to experience worsened sleep, some studies have shown that stimulant treatment of ADHD is associated with no change or even improvements in several sleep parameters, both in children [42, 43] and in adults [7, 16].

Amphetamine formulations with a typical duration of action of 12–16 h have been shown to not affect sleep on average in adults, as assessed using the Pittsburgh Sleep Quality Index (PSQI) [37, 44]. Surman and Roth [44] analyzed two large randomized, double-blind placebo-controlled trials of lisdexamfetamine and a mixed amphetamine salt formulation with up to 16 h of effect for shifts from good sleep at baseline to poor sleep and, based on PSQI, found no significant difference between drug and placebo. In both studies, approximately one-third of stimulant-treated patients showed improvements in sleep [44].

Optimal treatment of ADHD in adults targets symptoms through the entire day, prompting the development of a 16-h methylphenidate stimulant. PRC-063 (currently marketed as Adhansia XR[®] in the USA and as Foquest[®] in Canada) is a capsule containing identical multilayered beads composed of immediate-release and controlled-release layers of methylphenidate. Following ingestion, PRC-063 produces two distinct peak plasma concentrations: the first at ~1.5 h and the second at ~12 h. Steady state is reached by the third day of dosing [45, 46]. The safety, efficacy, onset, and duration of action of PRC-063 were previously investigated in adults with ADHD in a randomized, double-blind, placebo-controlled, crossover workplace environment study (NCT02225639) [46] and a randomized, double-blind, placebo-controlled, parallel-group adult laboratory classroom study (NCT03618030) [47]. Patients in both studies showed improved attention, assessed by Permanent Product Measure of Performance (PERMP) total score, averaged from 1 to 16 h post-PRC-063 dosing [46, 47]. Additionally, mean Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) combined score was improved during PRC-063 treatment compared with placebo treatment [46].

In a 4-week, randomized, placebo-controlled trial and a subsequent 6-month open-label extension study evaluating clinical efficacy and safety in adults [48], PRC-063 reduced symptoms in the double-blind study, as measured with the ADHD-5-Rating Scale (ADHD-5-RS) total score, with further improvement observed in the open-label study. Sleep quality was a secondary outcome in this pivotal trial.

The objective of the analyses reported here was to examine patient-reported sleep outcomes, as captured using the PSQI, in both the randomized controlled trial and the open-label extension in patients with ADHD treated with PRC-063. Since it has been commonly assumed that stimulants are associated with insomnia, and that the later in the day a stimulant is active the greater the potential effect on sleep, we hypothesized that PRC-063—which has been shown to be efficacious at 16 h in adult patients—would be associated with an increased rate of sleep problems [49].

2 Methods

2.1 Study Design

The present post-hoc analyses are based on a randomized, double-blind, forced-dose, placebo-controlled trial (NCT02139124) and an open-label extension study (NCT02168127) of the efficacy and safety of the extended-release methylphenidate hydrochloride formulation PRC-063 in adults with ADHD. Full details of the methods are provided elsewhere [48].

2.2 Participants

Participants, who provided written informed consent before any study-related procedures, were males and females aged ≥ 18 years with inattentive, hyperactive/impulsive, or combined presentation of ADHD (diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders-5*) and a total score of ≥ 24 on the ADHD-5-RS (a clinician-administered scale evaluating 18 symptoms of ADHD on a 4-point scale [0–3], with lower scores indicating less severe ADHD symptoms). Patients with an allergy to methylphenidate or amphetamines or a history of serious adverse reactions to methylphenidate or who were known to be non-responsive to methylphenidate treatment were excluded. Participants were also excluded if they had a psychiatric comorbidity (including sleep problems that were functionally impairing) that required use of other psychotropic drugs (including prescription sleep medications), as judged by the investigator. Patients were allowed to continue taking melatonin if they had been on a stable dose for at least 4 weeks.

2.3 Study Treatment

In the double-blind study, participants were randomized 1:1:1:1 to treatment with placebo or one of four fixed doses of PRC-063: 25, 45, 70, or 100 mg/day. Treatment consisted of 2 weeks of forced-dose titration followed by 2 weeks of maintenance on the randomized dose. The primary efficacy endpoint was clinician-rated ADHD-5-RS total score at the end of treatment for all PRC-063 doses combined versus placebo.

At the end of double-blind treatment, participants who continued to fulfill all the inclusion criteria and none of the exclusion criteria in the double-blind study were eligible to transition to a 6-month open-label extension study. Enrollment of eligible participants continued until half of the sample in the double-blind study had been enrolled in the open-label extension study. Patients who did not enter the open-label extension were followed-up for safety for 14 days after the end of double-blind treatment. In the extension

study, each patient's initial open-label PRC-063 dose was at the discretion of the investigator. Where necessary, a participant's dose was optimized via titration to 25, 35, 45, 55, 70, 85, or 100 mg/day. The maximum permitted dose was 100 mg/day. Participants who could not tolerate a dose of 25 mg/day were withdrawn. Each participant's daily dose was to be administered once daily upon waking, before leaving for work or school. Patients were followed-up for safety for 14 days after the end of open-label treatment.

2.4 Endpoints

The present analyses are based on endpoints from the double-blind and open-label studies: PSQI at baseline, the end of the double-blind study, and monthly visits during the 6-month open-label extension; spontaneously reported sleep-related AEs (defined as signs, illnesses, or experiences that developed or worsened in severity from baseline during the study), collected at all study visits; and Clinical Global Impressions-Severity (CGI-S) [50], assessed at baseline. The PSQI [51] is one of the most widely used self-rating instruments for sleep quality [52] and has been validated in adults with ADHD [3, 53]. It is designed to assess sleep quality during the previous month and comprises seven subscales: overall sleep quality, sleep latency, duration of sleep, sleep efficiency, sleep disturbance, requiring medication to sleep, and daytime dysfunction due to sleepiness. Each subscale is scored from 0 to 3 (where a lower score indicates better sleep quality). A global PSQI score (range 0–21) is calculated by summing the results for the seven subscales. In the present studies, global PSQI scores were also evaluated via a categorical analysis, where a global score of ≤ 5 indicated "good sleep" and a score of > 5 indicated "poor sleep" [51].

AEs were reported through the end of the safety follow-up period that followed open-label treatment or, for participants who did not transition to the open-label extension study, the end of the safety follow-up period that followed double-blind treatment.

2.5 Statistical Analyses

Data are presented as summary statistics. For PSQI scores, least squares (LS) mean change from baseline and LS mean difference between PRC-063 and placebo were calculated, and 95% confidence intervals were calculated for the LS mean difference between PRC-063 and placebo. All analyses were conducted using SAS version 9.2 or later. Statistical tests were two-sided, and P values ≤ 0.05 were considered statistically significant. No adjustment was made for multiple comparisons. Missing data were not imputed.

Scores for global PSQI and PSQI subscales at the end of double-blind treatment were compared between PRC-063 and placebo using two-sample t tests. Change from

baseline at the end of double-blind treatment was compared between PRC-063 and placebo by analysis of covariance with baseline score as a covariate. For patients enrolled in the open-label extension, global PSQI scores at the end of double-blind treatment and the end of open-label treatment were compared by paired t test. Finally, the proportion of patients who were good sleepers (global PSQI score ≤ 5) was compared between PRC-063 and placebo using Fisher's exact test.

Logistic modeling was performed, with the response variable being whether or not the patient reported poor sleep (global PSQI score > 5) at the end of double-blind treatment. The model contained seven predictor variables: study treatment (placebo and 25, 45, 70, and 100 mg/day PRC-063), sex, age (continuous), baseline global PSQI score (continuous), prior ADHD medication use (yes/no), body mass index (BMI; continuous), and ADHD type (combined, hyperactive-impulsive, and inattentive). A type 3 analysis of effects based on the Wald test was performed. Scatter plots of global PSQI score at the end of double-blind treatment versus global PSQI score at baseline were generated separately for patients who at baseline were classified as good sleepers (global PSQI score ≤ 5) or poor sleepers (global PSQI score > 5).

For patients treated with PRC-063, the association between ADHD response and sleep status at baseline and at the end of double-blind treatment was analyzed. ADHD responders were defined by a $\geq 30\%$ decrease in ADHD-5-RS score from baseline to the end of double-blind treatment [54]. Mean change in global PSQI score from baseline to the end of double-blind treatment in patients classified as good sleepers (global PSQI score ≤ 5) at the end of double-blind treatment was analyzed separately for ADHD responders and ADHD nonresponders.

For insomnia AEs occurring during double-blind treatment, summary statistics were calculated for duration of insomnia (for events that were resolved) and time of onset, categorized as day 1–7, day 8–14, day 15–21, day 22–28, or day 29–36. AEs were coded using *Medical Dictionary for Regulatory Activities* version 17.0.

3 Results

3.1 Disposition

In the double-blind treatment phase, 465 subjects were screened, and 375 patients with ADHD were randomized and treated: 297 with PRC-063 and 78 with placebo. Treatment was completed by 264 patients (88.9%) treated with PRC-063 and 69 patients (88.5%) treated with placebo. In total, 184 patients were enrolled and treated in the open-label extension study [48].

3.2 Demographics and Baseline Characteristics

All PRC-063 dose groups combined and the placebo group were evenly balanced in terms of age, sex distribution, race distribution, and BMI [48]. Most patients had combined-type ADHD: 74.7% for PRC-063 and 69.2% for placebo. Median (range) time since diagnosis of ADHD was 11 (0–57) years for PRC-063 and 10 (0–56) years for placebo. The PRC-063 and placebo groups were balanced in terms of disease severity based on CGI-S at baseline: mildly ill 2.7 versus 3.8%; moderately ill 48.8 versus 53.8%; markedly ill 45.1 versus 38.5%; and severely ill 3.4 versus 3.8%. No patients had a baseline CGI-S score of 1 (normal, not at all ill), 2 (borderline mentally ill), or 7 (among the most extremely ill patients). Although melatonin was allowed for patients who had taken a stable dose for at least 4 weeks prior to double-blind study entry, only 3% of patients in the PRC-063 group and 1.3% in the placebo group took melatonin during the trial. Use of other concomitant prescription sleep medications, such as zolpidem, eszopiclone, or temazepam, was considered a protocol violation and was infrequent (1.3% in the PRC-063 group and 2.6% in the placebo group).

3.3 Change in Global PSQI Score

Figure 1 shows the mean global PSQI scores during double-blind treatment and the open-label extension. In the double-blind study, a comparison between PRC-063 and placebo of LS mean change from baseline in global PSQI score at the end of treatment showed modest decreases (improvement) in both groups and no statistically significant differences

between groups ($P = 0.0972$; electronic supplementary material [ESM] 1). Decreases in global PSQI score were observed during the first month of open-label treatment and were maintained over 6 months. For patients enrolled in the open-label extension ($N = 184$), mean \pm SD global PSQI improved from 7.8 ± 3.55 at the end of double-blind treatment to 5.8 ± 3.11 at 1 month and 5.4 ± 3.21 at 6 months ($P < 0.0001$; ESM 1).

3.4 Changes in PSQI Subscale Scores

Scores for the seven PSQI subscales at the end of double-blind treatment and changes in subscale scores from baseline showed no statistically significant differences between patients who received placebo and patients who received PRC-063 (Table 1). A decrease (improvement) in mean sleep efficiency score from 1.9 at the end of double-blind treatment to 0.5 at 6 months was largely responsible for the observed decrease in mean global PSQI score during the open-label extension study (Fig. 1b).

3.5 Good and Poor Sleepers by Treatment

A score of 5 on the PSQI has been used as a cut off to distinguish good and poor sleepers [51]. In the double-blind study, the proportion of good sleepers at baseline was 20.9% for PRC-063 (all doses combined) and 23.1% for placebo. At the end of double-blind treatment, the proportion of good sleepers was 23.6% for all PRC-063 doses combined and 35.9% for placebo. During double-blind treatment, 14.0% of patients treated with PRC-063 went from being poor sleepers to good sleepers, whereas 9.4% of patients went from being

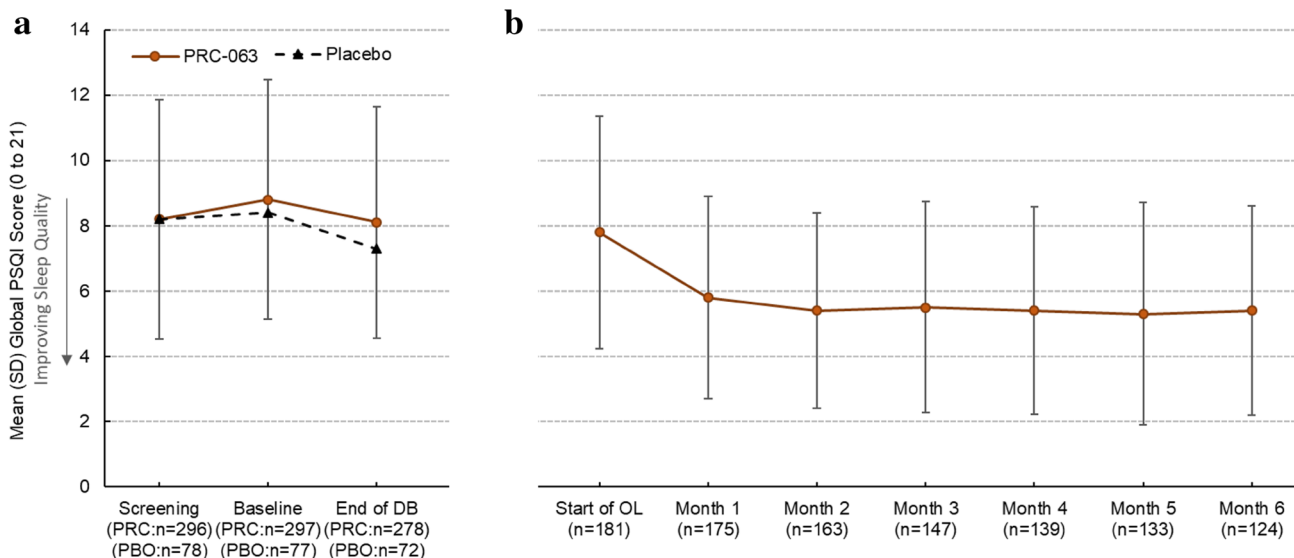


Fig. 1 Global Pittsburgh Sleep Quality Index (PSQI) score during **a** the double-blind (DB) study and **b** the open-label (OL) extension study. *PBO* placebo, *PRC* PRC-063, *PSQI* Pittsburgh Sleep Quality Index, *SD* standard deviation

Table 1 PSQI subscale scores at the end of the treatment period: double-blind treatment and open-label extension

PSQI subscale scores	Overall sleep quality	Sleep latency	Duration of sleep	Sleep efficiency	Sleep disturbance	Requiring medication to sleep	Daytime dysfunction due to sleepiness
Double-blind phase							
Placebo <i>n</i> = 72 ^a	Mean ± SD 1.0 ± 0.77	1.4 ± 1.04	0.6 ± 0.85	1.7 ± 1.39	1.3 ± 0.61	0.2 ± 0.76	1.1 ± 0.69
PRC-063 (all doses) <i>n</i> = 278 ^b	Mean ± SD 1.2 ± 0.68	1.4 ± 0.98	0.8 ± 0.95	1.9 ± 1.35	1.4 ± 0.59	0.3 ± 0.84	1.1 ± 0.71
	LS mean difference vs. placebo (95% CI)	0.1 (-0.1 to 0.3)	0.1 (-0.1 to 0.3)	0.2 (-0.2 to 0.5)	0.0 (-0.1 to 0.1)	0.1 (0.0-0.3)	0.0 (-0.1 to 0.2)
	<i>P</i> value ^c	0.5453	0.2756	0.3240	0.8556	0.1145	0.7772
Open-label phase							
PRC-063 (all doses) <i>n</i> = 124	Mean ± SD 1.0 ± 0.66	1.1 ± 0.95	0.6 ± 0.83	0.5 ± 0.92	1.1 ± 0.62	0.3 ± 0.71	0.8 ± 0.63

CI confidence interval, LS least square, PSQI Pittsburgh Sleep Quality Index, SD standard deviation

^a*n* for overall sleep quality = 71

^b*n* for overall sleep quality = 277

^cChange from baseline vs. placebo (analysis of covariance with baseline score as a covariate)

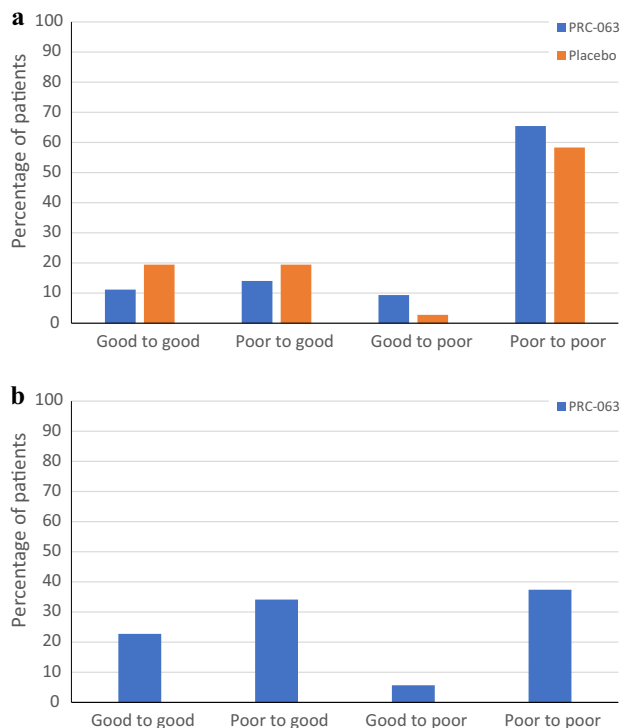


Fig. 2 Shift in sleep status during **a** the double-blind study and **b** the open-label extension study. Data show the shift in sleep status from baseline to end of study, where baseline for the open-label extension study is defined as the end of the double-blind study. Sleep status is based on global PSQI score, with a score of >5 indicating poor sleep and a score ≤5 good sleep. Data for sleep status at baseline and/or end of study were missing for 19 patients treated with PRC-063 in the double-blind study, six patients treated with placebo in the double-blind study, and 60 patients in the open-label extension study. Further information is provided in ESM 2. *PSQI* Pittsburgh Sleep Quality Index

good sleepers to poor sleepers; for the remaining patients, “good versus poor” sleep status did not change during double-blind treatment (Fig. 2a and ESM 2). For placebo, 19.4% of patients went from being poor sleepers to good sleepers, whereas 2.8% of patients went from being good sleepers to poor sleepers. Overall, 65.5% of patients who received PRC-063 and 58.3% of patients who received placebo were poor sleepers at both baseline and the end of double-blind treatment. For patients who entered the open-label extension study, a greater proportion of patients were good sleepers at 6 months than at the end of double-blind treatment (57.3 vs. 26.0%). Moreover, 34.1% of patients went from being poor sleepers to good sleepers, whereas only 5.7% of patients went from being good sleepers to poor sleepers (Fig. 2b).

Table 2 Time to onset and duration of insomnia adverse events during double-blind treatment

Insomnia characteristic ^a	PRC-063 (all doses) N = 297	Placebo N = 78
Duration of insomnia (days)^b		
<i>n</i>	49	3
Mean ± SD	14.5 ± 10.7	12.0 ± 10.1
Median	12	10
Minimum; maximum	1; 41	3; 23
Number of days of treatment prior to insomnia onset^c		
<i>n</i>	71	4
Mean ± SD	8.30 ± 7.03	12.50 ± 3.42
Median	7	12
Minimum; maximum	1; 32	9; 17
Days of treatment prior to onset of insomnia^c, <i>n</i> (%)		
1–7	39 (54.9)	0
8–14	16 (22.6)	3 (75.0)
15–21	14 (19.8)	1 (25.0)
22–28	1 (1.4)	0
29–36	1 (1.4)	0

SD standard deviation

^aIn this analysis, “insomnia” comprises adverse events of insomnia, initial insomnia, middle insomnia, and terminal insomnia

^bData are for adverse events that were resolved at end of study

^cStart day was calculated relative to the start of double-blind treatment

3.6 Predictors of Poor or Good Sleep at the End of Double-Blind Treatment

The results of a type 3 logistic regression analysis of effects based on the Wald test are displayed in ESM 3. Seven candidate predictors were tested for their ability to predict sleep quality (good vs. poor) at the end of the double-blind treatment: baseline global PSQI score, study treatment, sex, age, prior ADHD stimulant therapy, BMI, and ADHD subtype. Only baseline global PSQI score was identified as a statistically significant predictor of poor sleep at the end of double-blind treatment (odds ratio 1.491; 95% confidence interval 1.345–1.653; *P* < 0.0001). PRC-063 dose (including 0 mg/day for placebo) was not a statistically significant predictor (*P* = 0.1428). Similarly, sex, age, prior ADHD stimulant therapy, BMI, and ADHD subtype were not statistically significant predictors of poor sleep at the end of double-blind treatment. To further understand the contribution of baseline global PSQI score, scatter plots of global PSQI score at the end of double-blind treatment versus global PSQI score at baseline were created with regression lines. These show that

patients who were classified as good sleepers at baseline tended to remain good sleepers regardless of whether they received PRC-063 or placebo, whereas patients who were classified as poor sleepers at baseline and received PRC-063 treatment tended to show greater improvements in sleep quality than those who received placebo (ESM 4).

For patients treated with PRC-063, sleep status at the end of double-blind treatment was analyzed according to whether patients were ADHD responders (showed a $\geq 30\%$ improvement in ADHD-5-RS score from baseline to the end of double-blind treatment) or non-responders (ESM 5). At the end of double-blind treatment, 28% of ADHD responders and 20% of ADHD non-responders were good sleepers ($P = 0.1324$, Cochran–Mantel–Haenszel test). When only PRC-063-treated patients considered to have “good” sleep at the end of double-blind treatment were considered, ADHD responders had poorer sleep at baseline than ADHD non-responders (mean global PSQI score 6.6 vs. 5.2) (ESM 6). The mean improvement in global PSQI score from baseline to the end of double-blind treatment was 2.9 for ADHD responders and 1.2 for ADHD non-responders.

3.7 Incidence of Sleep-Related Adverse Events

Rates of insomnia (15.8 vs. 3.8%) and initial insomnia (6.1 vs. 1.3%) during double-blind treatment were higher for PRC-063 (all doses combined) than for placebo. When reports for all sleep-related AEs were combined, the rate was higher for PRC-063 than for placebo (23.6 vs. 5.1%). Moreover, two patients were withdrawn from the double-blind study because of insomnia AEs during PRC-063 treatment. Baseline global PSQI scores for these two patients, randomized to the 45 and 100 mg/day groups, were 1 and 8, respectively. During the open-label extension study, the rate of insomnia as an AE (15.1%) was lower than that during double-blind treatment. One patient (optimized dose of 45 mg/day) was withdrawn from the open-label extension study because of insomnia. The baseline global PSQI score for this patient was 11.

For PRC-063, 97.2% of the insomnia AEs were reported in the first 3 weeks of treatment (Table 2). For resolved insomnia events, the median duration was 12 days for PRC-063 and 10 days for placebo.

4 Discussion

In the double-blind study, there were no statistically significant differences in overall sleep quality (global PSQI score) or specific sleep difficulties (PSQI subscale scores) between active drug and placebo. In addition, in a logistic regression analysis, stimulant treatment was not a statistically significant predictor of poor sleep at the end of double-blind

treatment. After 6 months of open-label treatment, mean global PSQI had improved by 2.4 points compared with the end of double-blind treatment; the minimal clinically important difference for PSQI was previously estimated at 2.5 points [55]. This suggests that the improvement in sleep observed between the beginning and the end of open-label treatment was clinically meaningful. However, given that sleep also improved in the placebo group during the double-blind period, we cannot rule out the possibility that the continued improvement in the open-label group was not partially driven by an earlier placebo effect on sleep.

During double-blind and open-label treatment, greater proportions of patients with ADHD treated with PRC-063 went from being poor sleepers (global PSQI score > 5) to good sleepers (global PSQI score ≤ 5) than from good sleepers to poor sleepers. This was despite reported rates of insomnia AEs being higher in individuals receiving PRC-063 versus placebo, in agreement with a recent meta-analysis showing higher risks of insomnia AEs for pooled methylphenidate formulations versus placebo [41]. Taken together, these findings suggest that stimulant treatment may have beneficial effects on sleep in some patients and deleterious effects in others.

The only identified significant predictor of poor sleep at the end of double-blind treatment was the patient’s sleep status at baseline, as measured by global PSQI score. Patients who came into the study with sleep problems were more likely to have sleep problems at the end of the study. As noted, sleep problems are endemic in patients with ADHD. This suggests that clinicians can predict which patients are most likely to have sleep problems on stimulants by doing a sleep assessment before starting stimulant treatment. This aligns with ADHD practice guidelines recommending that clinicians assess sleep prior to treatment with stimulants [56]. These findings also indicate that research on sleep during stimulant treatment is meaningless if it does not control for baseline sleep difficulties. Our findings suggest that the inherent difficulties with sleep in patients with ADHD may be a stronger predictor of sleep quality outcome than they are of adverse sleep events. When clinicians provide patients with education about medications, they need to emphasize that, although some patients will experience insomnia-related AEs, they are likely to be short term, that many patients experience improvement in sleep quality over time, and that insomnia events are less likely if they are sleeping well prior to stimulant treatment.

Our findings on the association between sleep problems and ADHD symptomatology are consistent with previous studies of sleep and ADHD [36]. The proportion of good sleepers at the end of double-blind treatment showed a trend of being higher for patients classified as ADHD responders (based on change in ADHD 5-RS score) than for non-responders. This is consistent with sleep problems being

predicted by current presence of ADHD symptoms (ADHD state), rather than whether or not a patient has ever had ADHD symptoms (ADHD as a trait) [17]. When ADHD improved, so did sleep. This suggests that the presence of sleep problems in adults with ADHD is not solely based on a genetic trait but also on the predominant ADHD symptomatology and whether or not the patient is currently symptomatic. Further research would be necessary to reinforce this conclusion.

It is reasonable to consider that stimulants may have a deleterious effect on some aspects of sleep (such as sleep-onset latency) but a beneficial effect on other aspects of sleep such as daytime somnolence and that, as a result, total sleep scores may mask particular aspects of sleep impairment. Our results are not consistent with this hypothesis, in that we did not see a difference between stimulant and placebo for either overall sleep quality or particular PSQI subscales. However, sleep efficiency did improve during the open-label study, possibly because problems falling asleep and lack of overall sleep mean that patients maintain sleep when they do actually fall asleep. Nonetheless, no difference in sleep efficiency between PRC-063 and placebo was observed during the double-blind study. It is possible that the period of observation was insufficient or the sample of individuals with particular PSQI subscale patterns of sleep vulnerability was inadequate to truly characterize differential sleep effects of stimulant treatment.

Although PRC-063 was administered at doses up to 100 mg/day, the AE profile was within expectations for a methylphenidate ADHD medication, and significant difficulties in falling asleep or staying asleep were not generally observed. Moreover, the rate of insomnia as an AE during the open-label extension study of PRC-063 was comparable to that during double-blind treatment, despite the much longer period for AE reporting (6 months vs. 20–40 days). Furthermore, the median duration of resolved insomnia events during double-blind treatment was comparable for PRC-063 (12 days) and placebo (10 days). Our AE data suggest that, contrary to our hypothesis based on previous 12-h stimulant trials [40, 57], the 16-h duration of this product did not seem to be associated with increased insomnia AEs.

Our work extends and replicates findings for PRC-063 reported in an adult workplace environment study (NCT02225639) [46]. The study, which featured a 2-week double-blind crossover phase after PRC-063 dose optimization, found no significant difference between PRC-063 and placebo in terms of mean global PSQI score or mean PSQI overall sleep quality score during treatment. However, mean sleep duration was lower, and the rate of insomnia reported as an AE was higher, during treatment with PRC-063 versus placebo [46].

Our results for PRC-063 are also comparable to those from previous randomized, double-blind, forced-dose,

placebo-controlled studies of lisdexamfetamine and triple-bead mixed amphetamine salts, which showed no significant differences between active treatment and placebo in terms of meaningful changes in global PSQI score from baseline to end of treatment (4 weeks/6 weeks) [44].

The impact of stimulant treatment on sleep in adults with ADHD is complex. Outcomes in clinical trials may vary depending on medication variables (e.g., type of stimulant, duration of stimulant action) and aspects of trial methodology (e.g., method of assessment, time on drug, rate of titration). Importantly, although primary mood and anxiety disorders may be exclusion criteria in clinical trials, including the present studies, many patients with ADHD will have significant symptoms of depression, anxiety, or emotional dysregulation that contribute to sleep difficulty—perhaps to a greater extent than ADHD itself [58]. In real-world settings, guidance is available to assist practitioners in managing sleep issues while treating patients with ADHD [59].

Limitations of the present studies include the exploratory nature of the PSQI analyses. Although the double-blind study was powered to analyze the primary efficacy variable (clinician-rated ADHD-5-RS total score), it may not have been powered to detect significant differences in some sleep outcomes. Another limitation is the lack of adjustment for multiple comparisons. Moreover, too much data on start and end dates of insomnia AEs during the open-label extension study was missing to allow a meaningful analysis of duration of insomnia AEs, possibly because of the monthly nature of the clinic visits. This means that we do not know the extent to which sleep problems resolved over time.

While the PSQI is the most commonly used and thoroughly validated generic sleep measure [60] and captures heterogeneous dimensions of sleep, it provides a subjective assessment of sleep and has been validated more as a research tool than as a tool for clinical assessment. However, PSQI scores have been shown to correlate with objective actigraphic measurements [61, 62] and with other measures of sleep quality, such as clinical diagnosis of insomnia, Insomnia Severity Index total score, and polysomnography variables [60].

A further limitation of the study design is that nearly 90% of patients were over- or undermedicated during fixed-dose double-blind treatment with PRC-063 [48], which confounds direct generalization to treatment as usual in clinical practice, where dosing is individualized. This may also partly explain why further improvements in sleep were observed during open-label treatment, when doses could be optimized. Since sleep difficulty is a dose-related side effect, forced-dose randomization is not ideal for studies looking at sleep outcomes with stimulants. Patients receiving lower-than-optimal doses will underreport sleep difficulties, whereas patients receiving higher-than-optimal doses will overreport sleep difficulties. In this sense, the open-label

data, although uncontrolled, are a better reflection of clinical practice than the double-blind data. It is also of note that, in the placebo group, 19.4% of patients went from being poor sleepers to good sleepers. This may reflect the variability of sleep problems or that being in a clinical trial has a placebo effect on sleep. Repeated completion of the PSQI would be expected to make patients more aware of their sleep patterns and thus potentially lead to better sleep hygiene.

The open-label sample likely suffered from selection bias, because it can be assumed that patients who experienced insomnia or other sleep problems during double-blind treatment would be less likely to continue to the open-label study. Furthermore, the double-blind sample may have excluded potential participants who were known to be nonresponsive to methylphenidate and may therefore have been weighted toward responders.

A final limitation is that the use of sleep supplements and medications during double-blind and open-label treatment may have led to insomnia being underestimated. Although some patients may have been attempting to improve sleep-onset latency with melatonin or prescription sleep medications, the numbers of patients were small, so any effect on the study results was likely modest.

5 Conclusions

This analysis of PRC-063 study results has demonstrated that, even though insomnia is a common AE in clinical trials of stimulants in patients with ADHD, sleep was improved in some patients treated with PRC-063, and PRC-063 had no statistically significant effect on sleep in patients at the group level.

The prolonged release of PRC-063 provides patients with the option of a once-daily treatment that may endure into the evening without necessarily leading to long-term difficulty with insomnia and even potentially improving sleep. Given that the proportion of good sleepers was twice as high at the end of open-label treatment than at the end of double-blind treatment, when clinicians are discussing stimulant treatment with patients, they need to note that sleep can improve in some patients following stable treatment. The results of this study further challenge the common clinical assumption that stimulants disrupt sleep and that longer-acting stimulants reduce sleep quality in all patients. A more nuanced assessment is required.

Our analysis emphasizes the strong interindividual differences in sleep response to stimulant treatment, which may be particularly relevant for patients who have sleep difficulties prior to treatment. Further research designed to look at sleep outcomes with stimulant treatment as the primary objective could clarify how and why sleep improves in some patients. Close evaluation of the response of specific sleep variables

is needed to clarify our understanding of the complex relationship between sleep, ADHD, and stimulant treatment. To maximize their clinical relevance, future studies should use dose optimization and include comparison to placebo effects, with careful assessment of baseline sleep difficulties as a predictor.

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Declarations

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Ethics approval The studies were conducted in Canada and the USA in 2014–2015 in accordance with the Declaration of Helsinki, good clinical practice, and national and local laws. They were approved by a central institutional review board (IRB Services, Aurora, ON, Canada; now known as Advarra) or, if required, by a local institutional review board.

Consent to participate All participants provided written informed consent before any study-related procedures.

Consent for publication Not applicable.

Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions MW, MC, and GD were responsible for the conception or design of the work. GD and EH were responsible for data collection. MW, MC, and GD drafted the article. All authors were responsible for data analysis and interpretation, critical revision of the article, and final approval of the version to be published and agree to be accountable for all aspects of the work.

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