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Chapter 4

Positive effects of prolonged methylphenidate treatment on sleep in children with Attention-Deficit/Hyperactivity Disorder: a double-blind randomized controlled trial

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Abstract

Importance: Whether or not medication for Attention-Deficit/Hyperactivity Disorder (ADHD) affects sleep is a serious concern for parents and psychiatrists. So far, however, sleep effects of methylphenidate (MPH), the most commonly prescribed drug for ADHD, have only been studied in previously medicated children, or only for a brief period. Here, we assessed whether the prolonged use of MPH affects sleep. As it is comorbid with ADHD and also associated with sleep problems, we further investigated MPH effects on restless legs syndrome (RLS).

Methods: A 16 week double blind, placebo controlled, multicenter clinical trial with MPH in children (ePOD-MPH trial). 75 boys were screened for eligibility using DSM-IV criteria for ADHD (all subtypes). Additional inclusion criteria were; male sex, age 10-12 years and a medication-naive status. Sleep was assessed using actigraphy, diaries and questionnaires both prior to randomization, during the trial (week 8), and 1 week after trial end. RLS was assessed using a diagnostic interview and rating scales.

Results: 50 boys (mean age 11.4y, SD 0.9) were randomized to MPH or matching placebo. MPH (+4.94%; 95%CI, 1.18-8.70; p=0.005), but not placebo (+0.97%; 95%CI -2.40-4.33; p=0.868), significantly increased post-treatment sleep efficiency (time-by-treatment interaction effect $F(2,240)=5.07$, p=0.007). In addition, MPH promoted an earlier and faster sleep onset and increased the duration of sleep. No effects were found on RLS measures.

Conclusions: We found a positive effect of a 16 week MPH treatment on the efficiency, onset, and duration of sleep, but not on RLS, in boys with ADHD.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, impulsivity and poor concentration[1]. Methylphenidate (MPH) is the most prescribed stimulant medication for ADHD treatment, and is very effective in alleviating ADHD symptoms. MPH blocks the dopamine (DA) transporter, thereby increasing extracellular DA levels, which is thought to underlie the changes in behavioral symptoms[2]. Previous studies suggest a five-fold prevalence of sleep problems in children with ADHD compared to healthy children[3,4]. These problems include; high bedtime resistance, delayed sleep onset, frequent nocturnal awakenings and excessive daytime sleepiness[5–7]. However, it is poorly understood whether these sleep problems are a result of intrinsic ADHD symptoms, or the consequence of ADHD medication, and what neurobiological mechanisms underlie the sleep problems[8].

Although the possibility that sleep problems could be induced by ADHD medication forms a serious concern for parents and psychiatrists when considering pharmacotherapy[9,10], studies about effects of ADHD medications on sleep are scarce, and their results inconsistent. A recent meta-analysis on actigraphic sleep estimates in children with ADHD, concluded that MPH treatment delayed sleep onset, reduced total sleep time and lowered sleep efficiency when compared to placebo-treated patients[11]. However, an actigraphic study in adults with ADHD[12] rather suggested favorable effects of MPH whereas a polysomnographic sleep study in children with ADHD failed to find effects of MPH on sleep[13]. A lack of effect has also been reported in studies that used parental reports to compare sleep between stimulant-treated and untreated children with ADHD[14,15]. One possibility is that these conflicting findings may result from differences in treatment regimens, as treatment duration was typically short (e.g., 1-7 weeks), or from differences between the methods to measure sleep (actigraphy, polysomnography or questionnaires). Importantly, however, all prior studies included previously medicated patients, which makes it difficult, if not impossible to disentangle effects of ADHD per se from effects of previous medication on the sleep changes reported.

Next to sleep problems, restless legs syndrome (RLS) has a greater incidence in ADHD children and adolescents than in the general population[16]. RLS is a chronic neurological disorder that is often comorbid with ADHD, and may share a common dopamine deficit. RLS has further been found to be associated with sleep disorders such as insomnia and shares a common genetic

polymorphism with ADHD[17]. So far, effects of MPH on RLS in children with ADHD have never been investigated.

Therefore, we here investigated effects of MPH on sleep and RLS in a cohort of medication-naive ADHD children during a relatively long treatment period, on and off medication. These data were obtained from the ePOD-MPH trial (Effect of Psychotropic Drugs on the Developing brain) in which medication-naive children with ADHD were randomly assigned to treatment with either MPH or placebo for a period of 16 weeks[18]. Because sleep and RLS have been proposed to involve dopaminergic function[19], and as we found before prolonged increases in dopaminergic activity in these children[20], we hypothesized that lasting positive effects on sleep as well as on RLS may occur due to a reduced dopamine turnover rate. This is supported by a growing body of evidence from preclinical studies, reporting effects of early (peri-adolescent) MPH treatment on measures for dopamine turnover, like reductions in D3 receptor autoregulation[21] and altered dopamine transporter densities[22].

Methods

Trial design

The ePOD-MPH trial was a 16-week double-blind, randomized, placebo-controlled, multicenter trial with MPH in medication-naive children with ADHD with a blinded end-point evaluation[23]. The primary outcome measure of the ePOD-MPH trial was to report on the modification by age of MPH treatment on the outgrowth of the DA system using state-of-the-art Magnetic Resonance Imaging (MRI) techniques (pharmacological MRI, diffusion tensor imaging and resting state fMRI).

Our two secondary outcome measures were: a) to report on the modification by age of MPH on the outgrowth of the DA system, using several functional outcome measures (functional MRI (fMRI), neuropsychological test battery); which have already[23] and will be published elsewhere; and b) to report on the effects of MPH on RLS symptoms and sleep, which we report here. The current study was powered on the primary objective. Because the sleep data was often incomplete in the adults, only the children were included in this study, of whom complete data sets were available.

The trial protocol was registered by the Central Committee on Research Involving Human Subjects (an independent registry) on March 24, 2011 (identifier NL34509.000.10) and subsequently at The Netherlands National Trial Register (identifier NTR3103), with enrollment of the first patient on October 13, 2011. The institutional review board of the Academic Medical Center (AMC) approved the study. The trial ended on June 15, 2015, and was monitored by the Clinical Research Unit of the AMC. Written informed consent was obtained from the legal representatives of all participants.

Participants

Participants were 50 medication-naive boys (10-12 years old) recruited through clinical programs at the Departments of Child and Adolescent Psychiatry at Triversum (Alkmaar, the Netherlands) and De Bascule Academic Center for Child and Adolescent Psychiatry (Amsterdam, the Netherlands). All participants were diagnosed with ADHD according to the DSM-IV[24] by an experienced psychiatrist. The Diagnostic Interview Schedule for Children (authorized Dutch translation)[25] was used to confirm the diagnosis. Subjects with comorbid Axis-I psychiatric disorders requiring medication treatment, a history of major neurological or medical illness, or a history of clinical treatment with drugs influencing the dopaminergic system (e.g. stimulants, neuroleptics, antipsychotics, and DA receptor type 2 and 3 agonists) were excluded.

Intervention, randomization and blinding

Participants were randomly assigned to either MPH or placebo (PLAC) treatment for 16 weeks[26]. Their treating physician prescribed the medication (maximum dose of 60 mg in 1-2 doses daily) under double-blind conditions on clinical guidance (reduction in ADHD symptoms), in accordance with Dutch treatment guidelines. Parents of the children received psycho-education. Adherence to the study medication was monitored at 5 control visits (in week 1, 2, 3, 8, and 12).

Outcomes

Our main outcome measure was estimated sleep efficiency (SE) prior to-, during-, and one week after treatment discontinuation, assessed using actigraphy. SE best summarizes the quality, composition, continuity and consolidation of sleep[27]. Secondary sleep outcome measures were; sleep onset latency (SOL), total sleep time (TST), total in-bed time (TIB), objective and subjective sleep start time (SST and SST-SUBJ), objective and subjective final wake time (Wake time and Wake-subj), wake after sleep onset (WASO), number of wake bouts (WBnumber), mean wake bout time (WBmean), interdaily stability (IS), intradaily variability (IV), the amount of activity during the 5 hours with the lowest activity (L5) and during the 10 hours with the highest activity (M10), the amplitude of the sleep-wake rhythm (AMP) (Table 1).

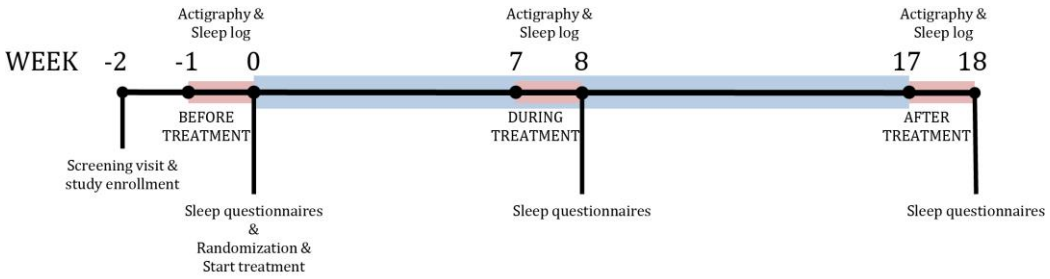
To obtain these data, subjects wore an Actiwatch AW4 (CamNtech Ltd., Cambridge, UK) on the non-dominant wrist for 24 hours/day for five consecutive nights at three time-points during the 16-week treatment: one week before randomization (baseline, BL), during the eighth week of treatment (during treatment, DT) and during the week after treatment, i.e. in week 17 (post-treatment, PT) (Figure 1). Actiwatch Sleep Analysis 5.0 Software (CNT, UK) was used to calibrate the actiwatches. Epoch length was set to 30 seconds. In addition, subjects were instructed to fill in a sleep-diary for five days during each actigraphy period. Data were analyzed using an in-house scripted algorithm (Supplementary Material).

In addition to actigraphic sleep estimates, multiple self-reported questionnaires were administered (Supplementary Material): the Holland Sleep Disorder Questionnaire (HSDQ), used to screen for sleep disorders at baseline and the Johns Hopkins telephone diagnostic interview for RLS (RLS-HTDI) to screen for RLS diagnosis at baseline. The Epworth Sleepiness Scale (ESS) and the Evaluation List Insomnia Therapy (ELIT) were assessed at all three time points as subjective sleep questionnaires. Severity of RLS during the trial was measured with the Johns Hopkins RLS severity scale (JHRLSS). ADHD symptom severity was assessed using the Disruptive Behavior Disorder Rating Scale (DBD-RS).

Table I. Sleep variable definitions

Variable	Definition
Actigraph-based sleep estimates	
Sleep efficiency (SE)	The objective total sleep time divided by the objective time in bed, multiplied by 100 (%)
Sleep onset latency (SOL)	The time it took the subject to fall asleep: time between lights off time (diary) and objective sleep start time (min)
Total sleep time (TST)	The total time period scored as 'sleep' between objective sleep start time and objective final wake time (min)
Total in-bed time (TIB)	Time between in bed time (diary) and out of bed time (diary) (min)
Sleep start time (SST)	The objective time when the subject fell asleep (time)
Final wake time (Wake time)	Objective time when the subject woke up in the morning (time)
Wake after sleep onset (WASO)	The total time period scored as 'wake' between the objective sleep start time and the objective final wake time (min)
Number of wake bouts (WBnumber)	Number of continuous blocks, one or more 'wake' epochs in duration, between the objective sleep start time and the objective final wake time (number)
Mean wake bout time (WBmean)	'Wake after sleep onset (WASO)' divided by the 'number of wake bouts (WBnumber) (min)
Subjective diary-based sleep estimates	
Subjective sleep start time (SST-SUBJ)	The subjective time when the subject turned off the lights to go to sleep (time)
Subjective final wake time (Wake-SUBJ)	The subjective time when the subject woke up in the morning (time)
Actigraphic rest-activity rhythm variables	
Interdaily stability (IS)	The predictability of the 24-h rest-activity pattern
Intradaily variability (IV)	The fragmentation of the activity profile into brief periods of rest and activity
Activity during 5 hours with lowest activity (L5)	The amount of activity in the 5 hours with the lowest activity
Onset time of L5 (L5 onset)	The objective time when the 5 hours with the lowest amount of activity started
Activity during 10 hours with highest activity (M10)	The amount of activity in the 10 hours with the highest activity
Onset time of M10 (M10 onset)	The objective time when the 10 hours with the highest amount of activity started
Amplitude of the sleep-wake rhythm (AMP)	Amplitude of the sleep-wake rhythm, calculated non-parametrically by subtracting L5 from M10

Figure 1. Study design
Timeline of the study. Blue bar represents treatment period. Red bars represent sleep measurement periods using the actigraph.



Statistical analysis

All analyses were intention-to-treat, with significance level set at $p<0.05$ (2-sided). A linear mixed model (using SPSS 22.0 (IBM, 2013)) was used to estimate the time-by-treatment interaction effect. An autoregressive covariance matrix was assumed, with a fixed intercept and the model was estimated using maximum likelihood. The targeted sample size for the ePOD RCT was based on the primary outcome measure of the RCT[26]. Follow-up pairwise comparisons were corrected for multiple testing using Sidak's correction. As some subjects used melatonin (BL, DT and PT n=9) and/or wore the actigraph during holiday periods (BL n=5, DT n=10, PT n=8), these variables were added to the model as dummy-coded covariates. Furthermore, JHRLSS scores were added as covariate. Missing values for this covariate (18.80% at BL, 22.90% DT and 20.80% PT) were replaced using logistic regression imputation based on condition, age and JHRLSS score at the two other time-points.

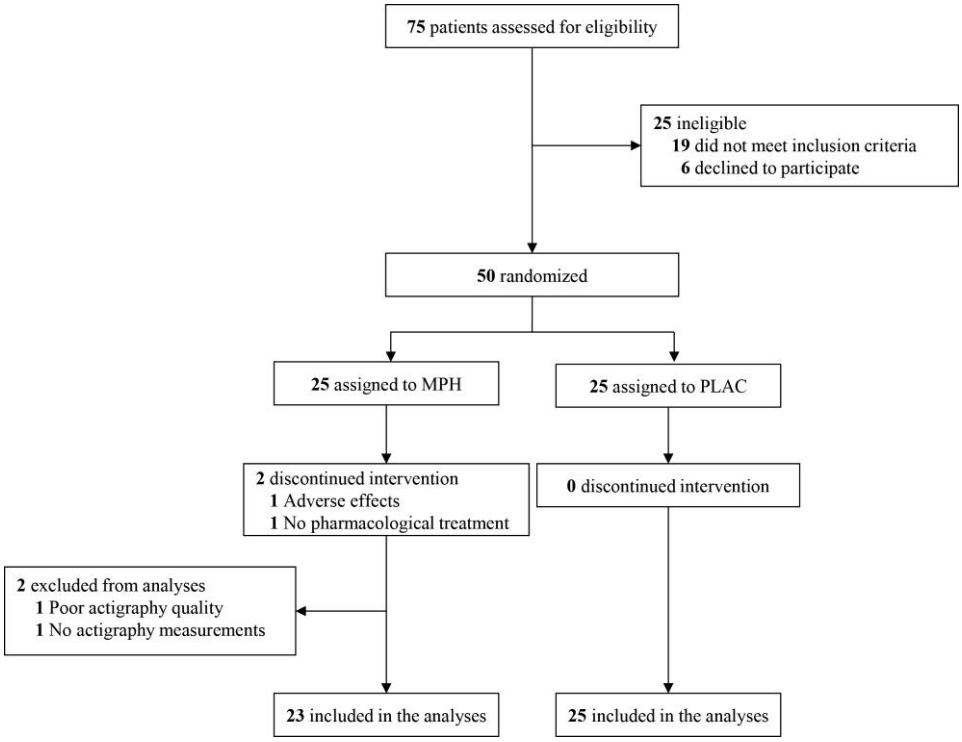
For the sleep variables that were calculated per day (SE, SOL, TST, SST, SST-SUBJ, TIB, Wake time, Wake-SUBJ, WASO, WBnumber, WBmean), days were added as a secondary repeated variable to the model. The ESS and ELIT subscore variables were not normally distributed and therefore log-transformed. Exploratory analyses were performed to assess possible correlations between the sleep variables and to distinguish between- from within-subject effects (Supplementary Material).

Results

Randomization and baseline characteristics

75 children were screened for study inclusion. 50 subjects met the inclusion criteria and were randomly assigned (1:1) to receive either MPH or placebo treatment (Figure 2). Baseline characteristics of the two groups are reported in Table 2. DBD-RS scores of attention and hyperactivity did not differ between the two randomization groups at baseline (attention p=0.20, hyperactivity p=0.61). No differences were found in baseline RLS diagnosis between the two groups (chi-square p=0.19). According to the HSDQ, severe sleep problems were absent from our sample at baseline. Adherence to the trial medication did not differ between the two randomization groups (mean MPH 84.89%, PLAC 79.68%, p=0.31). The final titrated dose in the placebo group was higher than the one prescribed in the PLAC group, but this difference was not statistically different (mean MPH 29.13 mg, mean PLAC 34.40 mg, p=0.07).

Figure 2. Consolidated Standards of Reporting Trials Flow Diagram
MPH, methylphenidate condition; PLAC, placebo condition



Main outcome measure SE

Due to logistical problems, sleep data was missing from 2 patients. Linear mixed model analysis showed a significant time-by-treatment interaction effect on our primary outcome variable SE ($F(2,240)=5.07$, $p=0.007$). MPH induced an increase in SE after trial-end when compared to baseline (mean difference 4.94%; 95%CI, 1.18-8.70; $p=0.005$). Also, the MPH condition had higher SE values than the placebo condition (mean difference 5.84%; 95%CI, 2.79-8.88; $p<0.01$). At baseline and during treatment (week 8), no differences were found in SE between the MPH and placebo condition (BL, mean difference 0.07%, 95%CI -2.88-2.74, $p=0.962$; DT, mean difference 0.11%, 95%CI -2.81-3.03, $p=0.94$)(Figure 3 and Supplementary Table I). Addition of the covariates holiday, melatonin and RLS to the model did not affect our results, although both holiday and melatonin had a main negative effect (holiday $F(1,219)=4.47$, $p=0.04$, melatonin $F(1,145)=17.68$, $p<0.01$).

Table II. Baseline demographics and characteristics of the study subjects

Variable	MPH n=23	placebo n=25
Demographics		
Age (y), mean (SD)	11.44 (0.80)	11.29 (0.93)
Estimated IQ, mean (SD)	103.22 (21.01)	103.35 (15.05)
ADHD symptom score, mean (SD)		
DBD-RS Attention	21.48 (3.29)	22.72 (3.31)
DBD-RS Hyperactivity	15.13 (5.08)	16.00 (6.49)
RLS		
RLS-HTDI diagnosis, No.		
Definite RLS	1	0
Possible RLS	3	0
Probable RLS	2	2
No RLS	17	23
Sleep problems		
HSDQ[a], No.		
Insomnia	0	1
Hypersomnia	0	0
Parasomnia	0	2
SBD	0	0
CRSD	0	0
RLS	2	3

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CRSD, circadian rhythm sleep disorder; DBD-RS, disruptive behavior disorder rating scale; HSDQ, Holland sleep disorder questionnaire; IQ, Intelligence quotient, measured using the Wechsler Intelligence Scale for Children; RLS-HTDI, John Hopkins telephone diagnostic interview for RLS; SBD, sleep-related breathing disorder

[a] 5 missing values for HSDQ (MPH n=4 and placebo n=1)

Secondary outcome measures

Significant time-by-treatment interaction effects, or main effects of time or treatment, were found for our secondary outcome variables SOL, TST, SST, Wake time, Wake-SUBJ, M10 onset and L5. Significance values and post-hoc comparisons for these sleep variables are presented in Figure 3 and Supplementary Table I and II. All these variables demonstrated positive effects in the MPH condition at trial end when compared to baseline values as well as to the placebo condition. The addition of the covariates did not affect these results, although a time-by-treatment interaction effect for WASO was apparent after addition of the covariates, and not before (Figure 3 and Supplementary Table I and II).

For the ELIT sleep subscore as well as for the ELIT wake subscore, we observed a main effect of time, indicating reduced sleep complaints during the trial in both treatment conditions. For ESS, we only observed a main effect of treatment, which was the result of a decreased excessive daytime sleepiness induced by MPH when compared to the placebo condition (Supplementary Table III and Supplementary Figure 1).

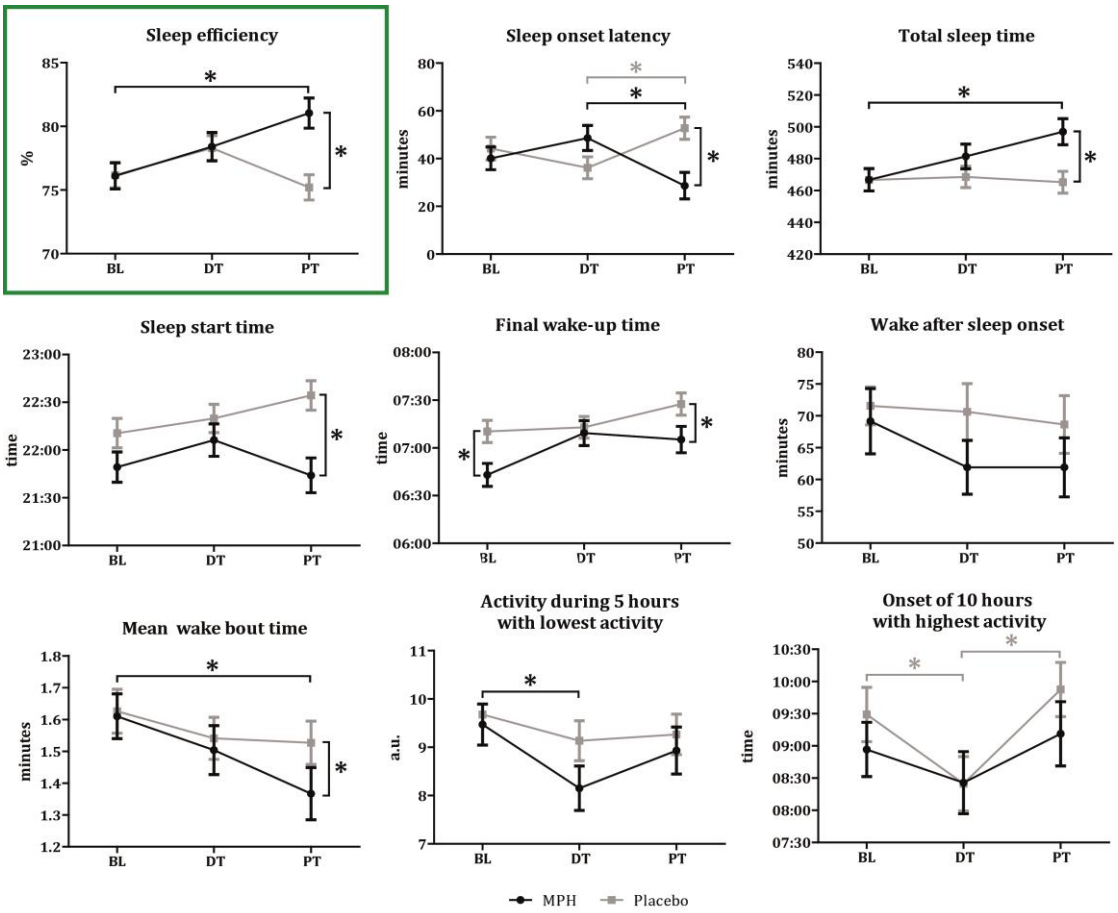
RLS and ADHD symptom severity

For RLS severity scores, we did not find a time-by-treatment interaction term (Wald chi-square=0.11, p=0.95), nor a main effect of time (Wald chi-square=0.16, p=0.93) or treatment (Wald chi-square=0.32, p=0.57). Additional analyses for the three individual timepoint failed to show significant differences in RLS severity scores between the two groups (BL chi-square p=0.92, DT chi-square p=0.88, PT chi-square p=0.88).

We further observed a significant time-by-treatment interaction ($F(2,87)=3.33$, $p=0.04$) on attention symptom severity, indicative of lower symptoms scores in the MPH condition compared to placebo during and after treatment (mean difference DT 4.64, 95%CI 2.14-7.15, $p<0.01$, mean difference PT 4.61, 95%CI 2.23-6.98, $p<0.01$). Additionally, in both conditions, the attention symptom severity was lower during treatment and at trial-end compared to baseline (DT vs. BL; MPH, mean difference 8.62, 95%CI 6.19-11.06, $p<0.01$; PLAC, mean difference 5.29, 95%CI 2.98-7.60, $p<0.01$; PT vs. BL; MPH, mean difference 8.5, 95%CI 6.42-10.58, $p<0.01$; PLAC, mean difference 5.14, 95%CI 3.15-7.13, $p<0.01$). For hyperactivity scores, only a main effect of time was found ($F(2,82)=23.09$, $p<0.01$), indicating decreased hyperactivity scores in both

conditions during treatment and post-treatment when compared to baseline (DT vs. BL; mean difference 4.7, 95%CI 2.98-6.43, p<0.01; PT vs. BL; mean difference 4.62, 95%CI 2.48-6.76, p<0.01).

Figure 3. Results sleep variables
Graphical representation of the sleep variable outcomes for the two conditions on three timepoints (BL, baseline; DT, during treatment; PT, post-treatment). Asterisks indicate a significant difference between the two conditions (p<0.05). Values represent means per condition for each time point, bars represent the standard error of the mean. Black lines indicate the MPH treated subjects, grey lines the placebo treated subjects.



Discussion

In this RCT, we investigated the effects of 16 weeks of MPH treatment on various sleep measures in medication-naive boys diagnosed with ADHD. MPH was found to significantly improve objective sleep quality one week after trial end; the children slept more efficiently, had a shorter sleep onset latency and slept longer as compared to both the placebo condition and baseline. Participants in both the placebo and MPH condition also answered more positively on the subjective sleep questionnaires. Additionally, MPH improved the ADHD symptom severity attention subscores, next to an improvement on the hyperactivity subscores in both the MPH and placebo conditions. In line with our hypothesis, the positive effects of MPH on sleep outlasted drug clearance as they were measured one week after treatment cessation. However, no effect of MPH on RLS was noted, neither in children nor in the adults.

Our findings of a strong, positive effect of prolonged MPH treatment on several sleep variables in boys with ADHD, differ from previous studies reporting that MPH worsens sleep, based on increases in SOL, decreases in SE and increased number of wake bouts[5,7]. Most of these studies, however, involved children that were prior medicated. The inclusion of medication-naive subjects in our current study is a crucial element in its design, as this excludes any possibly interacting effects of prior medication, that could have influenced the sleep measures in previous studies. The current positive effects were present one week after treatment cessation, indicating that MPH effects on sleep outlast the acute effects of the drug. This finding is consistent with preclinical literature[21,22] and with changes we found earlier in DA function, that also outlasted MPH treatment in humans[28]. The current enduring effects of MPH treatment on sleep may reflect neurochemical imprinting, that could result from MPH-induced changes in the developing DA system.

Also different from our current design, most prior studies on MPH treatment and sleep had a relatively short treatment duration (i.e., 1 to maximum 7 weeks). Interestingly, in a recent meta-analysis, the negative effects of stimulant exposure on SE decreased when ADHD medication was used for a longer period of time (max 7 weeks)[29]. In line with this, we also failed to find an effect of MPH on SE during treatment (in week 8). It is thus possible that at that time, the MPH dose was either not yet optimally titrated[30] and/or effects on sleep develop relatively slow. An additional explanation for our current findings is that the positive MPH effects on ADHD symptoms (e.g. the reduction in attentional problems during the day) might also have affected sleep indirectly. The increased ability to concentrate

during the day and the decreased day-time sleepiness, could have resulted in an increased build-up of 'sleep pressure' which would be expected to improve sleep quality at night.

When considering sleep quality in ADHD, the current positive effects of MPH can be interpreted within the framework of the sleep/wake cycle model of Borbély[31] and Schwartz and Roth[8]. This model proposes two processes, i.e. a process S (sleep) and a process C (circadian), that interact to regulate sleep. Process S is defined as the sleep pressure[8], while process C is defined based on a circadian rhythm[31]. As sleep problems in children with ADHD have been previously attributed to changes in either process S[32] or C[33], an increase in SE could be due to changes in either process. However, based on our significant effects of MPH on SE, SOL, TST, SST and wake time, and due to a lack of effects on the M10 and L5 circadian rhythm sleep variables, it is more likely that particularly process S is involved in the current effects of MPH on sleep quality in ADHD.

Sleep regulation is modulated by dopaminergic projections that promote wakefulness during the day by suppressing inhibitory projections to wake-promoting regions. Sustained wakefulness leads to a build-up of adenosine-related sleep pressure during day time, which subsequently promotes sleep[8,31]. As we have previously demonstrated that MPH treatment induces a lasting increase in dopamine function in the same ADHD boys as investigated here[28], it is tempting to suggest that sleep improvements may be related to a reduced dopamine turnover rate. This is consistent with preclinical studies reporting (age-dependent) reductions in dopamine turnover rate (e.g., reductions in D3 receptor autoregulation[21] as well as dopamine transporter densities[22]).

We did not find an effect of MPH on RLS and a possible explanation for this could be that there were not enough subjects with an RLS diagnosis in our sample at baseline: only 17% according to the RLS-HTDI. In a study done by Picchietti et al (2009), 64% of children with ADHD were estimated to suffer from RLS as judged by their nocturnal periodic limb movement[16]. The use of an RLS questionnaire in our study instead of polysomnography as used in the Picchietti study might have led to an RLS underdiagnosis in our cohort. Future studies focusing on the effect of MPH on RLS should take this into consideration.

The positive results of our RCT are of considerable clinical relevance, as effects on sleep are an important concern for parents and psychiatrists when discussing the prescription of MPH to children[10,34]. In view of the shorter treatment periods in prior studies, our findings suggest that when sleep problems occur shortly after treatment onset, it might be better to continue treatment at least until

several weeks, i.e. when an optimal drug titration has been established. Additional studies are needed to further establish the optimal time frame for sleep-related effects of MPH. Indeed, adaptations of DA function in response to MPH treatment may take multiple weeks[35], and therefore the (positive) effects of MPH on sleep may also require a substantial period of time before they become evident.

There are also some limitations to our study. First, we only included boys of around 11 years old and it remains to be demonstrated whether our findings can be generalized to females and other age groups. Secondly, some subjects received melatonin during the measurement periods (n=9 for all three timepoints). As melatonin is known to positively affect sleep[33], it is a potential confounder. However, we found a negative main effect of melatonin on SE, SOL, WASO, WBmean, and IV, while addition of melatonin as a covariate to our statistical model did not affect the main results and is therefore unlikely to have influenced our conclusion. Another limitation is despite the randomization, baseline and follow-up wake time differed between the two conditions. Since wake time was significantly longer during a holiday than during a school-week (p=0.009), we evaluated whether treatment groups were differentially measured during holidays. This was however not the case (at baseline: MPH n=2, placebo n=3; at follow-up: MPH, n=4, placebo n=4) and adding holiday to the model also did not alter our findings. A third limitation is that, according to the HSDQ, no severe sleep problems were present in our sample. Future studies are needed to investigate whether the current positive effects of MPH on sleep can also be generalized to children with ADHD suffering from severe, DSM-IV-related, sleep problems.

Conclusion

16 weeks of MPH increased the efficiency and duration of sleep and facilitated an earlier and faster sleep onset in ADHD boys of around 11 years of age when compared to the placebo condition. Hence, in line with our hypothesis, these findings indicate that MPH treatment in children has no negative effects on sleep but rather improves it. We did not detect an effect of MPH on RLS. As MPH-related sleep problems are an important concern for parents and treating physicians when discussing pharmacotherapy, the positive effects of MPH on sleep are of considerable clinical relevance to this field.

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Supplementary Material

Randomization

Randomization occurred using an in-house developed randomization program (Clinical Research Unit, Academic Medical Center Amsterdam). Patients were randomly assigned to either treatment (1:1) using a permuted block randomization scheme. Allocation was concealed for all parties. Placebo and MPH tablets were similar in appearance and were manufactured according to Good Manufacturing Practice criteria. After study end, blinding was checked with the patient and his psychiatrist as well as the study investigators.

Actimetry methods

The actimetry sensor of the ActiWatch measures the gross motor activity of the wrist, with high sensitivity to a palmar-dorsal movement (z-axis). Raw ActiWatch data were extracted and transformed into raw 3-dimensional accelerometry data in the unit of counts and were analyzed using MATLAB[1] using the Oakley algorithm[2]. In short, a 3-11 Hz band-pass filter was applied prior to sampling at 50 Hz and the data were converted to 128 bins between 0 and 5 with a resolution of approximately 25 counts/g. Any negative values were set to zero and residual baseline noise was removed. The signal was then converted to unit counts by taking the peak value of each second and summing across the epoch length (i.e. 30 sec). For identifying immobile-mobile (or sleep-wake) pattern, the threshold for MOBILE was set to a medium sensitivity for a window period of 10 minutes so that the algorithm scores any first 10-minute period with more than 1 mobile epoch with activity counts exceeding threshold as MOBILE (or wake). Therefore, the algorithm accommodates only 1 mobile epoch for the given time window during the estimation of sleep onset time and latency. The sleep logs were entered into the program to obtain the subjective sleep parameters for analysis.

Questionnaires

The Holland Sleep Disorder Questionnaire (HSDQ) was used only before start of the treatment as a screening instrument for sleep disorders (insomnia, sleep-related breathing disorder, hypersomnia, circadian rhythm sleep disorder, parasomnia and sleep-related movement disorders).[3] The John Hopkins telephone diagnostic interview for restless legs syndrome (RLS-HTDI) was used only before

start of the treatment as a screening instrument for RLS diagnosis[4]. The Johns Hopkins RLS severity scale was used to measure RLS severity during the trial[5]. The Epworth Sleepiness Scale (ESS) was used at all three time points as an assessment of measuring daytime sleepiness[6]. The ESS is a self-administered questionnaire with 8 items on a 4-point scale (0-3). A score of 11 or higher represents increasing levels of excessive daytime sleepiness. The Evaluation List Insomnia Therapy (ELIT) was conducted at all three time points to assess mood changes, and sleep and wake complaints[7]. The ELIT is also a self-administered questionnaire with 19 items on a 5-point scale (0-4). Three factor scores can be calculated: mood loss, sleep complaints and wake complaints. The Disruptive Behavior Disorder Rating Scale (DBD-RS) was used to assess disruptive behavior disorders[8].

Exploratory correlations

Exploratory correlation analyses for several of the sleep variables that were calculated for each day separate were performed in order to distinguish between within and between subject effects[9].

On all time points, a negative correlation was found between SE and SOL for within subject effects, indicating that subjects with mean lower SOL also show a mean higher SE (baseline β=-0.461, $p<0.001$, during treatment β=-0.540, $p=<0.001$, post treatment β=-0.615, $p<0.001$). In addition, between subjects effects on SOL were also negatively correlated to SE, showing that a lower SOL itself also correlates with a higher SE (baseline β=-0.486, $p=<0.001$, during treatment β=-0.416, $p<0.001$, post treatment β=-0.472, $p<0.001$). Addition of group and holiday to this model did not affect these results.

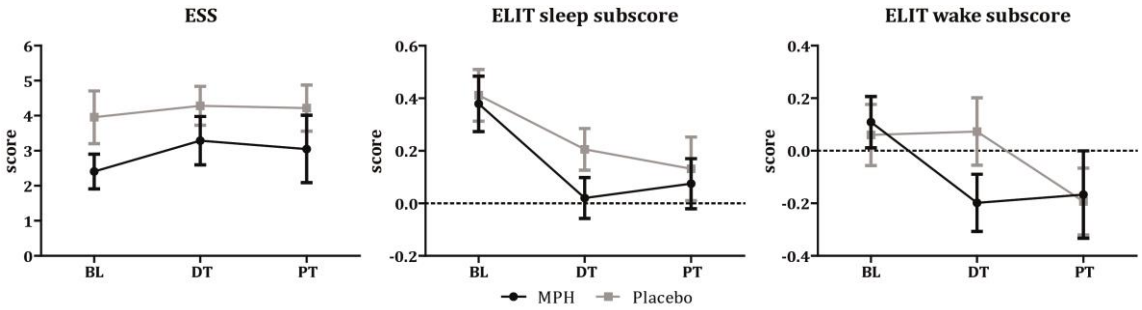
Second, a positive correlation was found on both the within and between subjects effects of TST on SE on all time points (Within subject effects: baseline β=0.542, $p<0.001$, during treatment β=0.570, $p<0.001$, post treatment β=0.642, $p<0.001$. Between subject effects: baseline β=0.386, $p<0.001$, during treatment β=0.343, $p<0.001$, post treatment β=0.462, $p<0.001$). A mean increase in TST correlates with a mean increase in SE (between subjects effect), and an increase in TST correlates with an increase in SE (within subject effect). Addition of group and holiday did not affect these results.

Third, on baseline and after treatment, an increase in SST was associated with an increase in SE (within subjects effect, baseline β=0.224, $p=0.002$, post

treatment β=0.245, p=0.001). Addition of group and holiday did not affect these results.

Lastly, on all time points, an increase in final wake time correlates with an increase in SE (within subjects effect, baseline β=0.316, p<0.001, during treatment β=0.347, p<0.001, post treatment β=0.338, p<0.001). Addition of group and holiday did not affect these results.

Supplementary Figure 1. Results Sleep Questionnaires
Graphical representation of the sleep questionnaire outcomes for the two groups on three time points (BL, baseline; DT, during treatment; PT, post-treatment). Only sleep questionnaire variables with significant post-hoc tests are shown. Values represent means per group for each time-point, bars represent the standard error of the mean. Black lines indicate the MPH treated subjects, grey lines the placebo treated subjects.



Supplementary Table I. Mean and standard deviations per group per time-point for all sleep- and ADHD-related variables.

	BL		DT		PT	
Variable	**MPH**	**PLAC**	**MPH**	**PLAC**	**MPH**	**PLAC**
SE (SD), %	76.33 (8.38)	76.15 (6.28)	78.49 (7.80)	78.59 (7.23)	80.59 (7.55)	75.17 (10.48)
SOL (SD), min	39.71 (41.14)	42.83 (35.02)	48.34 (36.10)	35.88 (29.78)	31.98 (34.79)	52.14 (52.95)
TST (SD), min	467.52 (59.73)	466.68 (53.88)	481.33 (50.02)	470.06 (54.11)	495.91 (56.34)	465.09 (77.30)
TIB (SD), min	612.63 (55.78)	613.67 (57.80)	614.43 (42.26)	599.08 (59.99)	616.89 (49.32)	618.96 (61.64)
SST (SD), time	21:03 (3:45)	20:47 (5:02)	21:48 (2:35)	21:48 (3:04)	21:27 (2:37)	19:44 (6:33)
Wake-time (SD), time	6:43 (0:50)	7:10 (0:49)	7:09 (0:50)	7:13 (0:48)	7:03 (0:42)	7:26 (1:14)
WASO (SD), min	68.99 (27.22)	71.78 (19.81)	62.27 (21.69)	68.39 (27.69)	61.41 (26.16)	69.30 (26.73)
WBnumber (SD), #	43.66 (12.11)	46.19 (11.73)	41.94 (12.78)	44.28 (15.94)	44.10 (12.80)	44.76 (14.37)
WBmean (SD), min	1.59 (0.51)	1.60 (0.45)	1.50 (0.51)	1.52 (0.56)	1.39 (0.50)	1.56 (0.55)
SST-SUBJ (SD), time	21:03 (0:44)	20:32 (4:05)	21:17 (0:42)	21:25 (2:16)	21:15 (0:51)	20:02 (4:58)
Wake-SUBJ (SD), time	7:08 (0:53)	7:35 (0:48)	7:23 (0:49)	7:33 (0:47)	7:21 (0:42)	7:54 (1:10)
IS (SD)	0.75 (0.15)	0.74 (0.16)	0.76 (0.11)	0.76 (0.13)	0.76 (0.16)	0.73 (0.15)
IV (SD)	0.38 (0.07)	0.36 (0.09)	0.40 (0.09)	0.37 (0.06)	0.38 (0.08)	0.35 (0.06)
L5 (SD), #	9.48 (2.04)	9.55 (1.90)	8.21 (1.54)	9.11 (2.20)	8.92 (2.30)	9.38 (1.79)
L5 onset (SD), time	14:18 (10:40)	17:38 (9:21)	17:26 (9:43)	16:26 (10:01)	18:31 (8:40)	16:43 (9:44)
M10 (SD), #	53.76 (4.43)	53.25 (5.62)	54.33 (4.06)	54.44 (4.48)	53.37 (5.65)	53.96 (4.89)
M10 onset (SD), time	8:56 (1:37)	9:29 (2:05)	8:25 (1:25)	8:25 (1:36)	9:11 (2:43)	9:52 (2:15)
AMP (SD)	44.29 (4.71)	43.70 (5.85)	46.11 (4.18)	45.32 (4.37)	44.46 (5.09)	44.58 (4.64)
ELIT mood (SD), score	1.49 (0.30)	1.40 (0.40)	1.35 (0.29)	1.31 (0.35)	1.37 (0.41)	1.26 (0.26)
ELIT sleep (SD), score	1.17 (0.54)	1.13 (0.53)	0.72 (0.35)	0.95 (0.41)	0.81 (0.44)	0.85 (0.62)
ELIT wake (SD), score	0.53 (0.47)	0.40 (0.60)	0.17 (0.52)	0.42 (0.68)	0.20 (0.79)	0.13 (0.65)
ESS (SD), score	2.61 (2.48)	3.75 (3.69)	2.79 (2.90)	4.30 (2.78)	3.06 (4.44)	4.10 (3.31)
DBD-RS Attention (SD), score	21.48 (3.29)	22.72 (3.31)	12.48 (5.49)	17.48 (3.08)	12.95 (4.85)	17.57 (4.67)
DBD-RS Hyperactivity (SD), score	15.13 (5.08)	16.00 (6.49)	9.42 (4.38)	12.57 (6.40)	9.71 (4.44)	12.52 (6.19)
JHRLSS (SD), score	0.68 (1.095)	0.49 (0.972)	0.70 (1.066)	0.60 (1.043)	0.68 (1.053)	0.58 (1.015)

Abbreviations: AMP, amplitude of the sleep-wake rhythm; BL, baseline; DBD-RS, disruptive behavior disorder rating scale; DT, during treatment; ELIT, evaluation list insomnia therapy; ESS, Epworth sleepiness scale; IS, interdaily stability; IV, intradaily variability; JHRLSS, Johns Hopkins restless leg syndrome severity scale; L5, activity during 5 hours with lowest activity; L5 onset, onset time of L5; M10, activity during 10 hours with highest activity; M10 onset, onset time of M10; PT, post-treatment; SD, standard deviation; SE, sleep efficiency; SOL, sleep onset latency; SST, sleep start time; SST-SUBJ, subjective sleep start time; TIB, total in-bed time; TST, total sleep time; Wake-SUBJ, subjective final wake time; Wake-time, final wake time; WASO, wake after sleep onset; WBmean, mean wake bout time; WBnumber, number of wake bouts

Supplementary Table II. Linear mixed model results for the secondary sleep variables (fixed effects)

Variable	Interaction effect Time * Treatment	Main effects Treatment	Time	Holiday	RLS	Melatonin	Significant post-hoc effects[A]
SOL	F(2,228)=3.02 P=0.003						PT: MPH > PLAC; MPH: PT < DT; PLAC: PT > DT
SOL + covariates	F(2,224)=7.05 P=0.001			F(1,207)=1.62 P=0.204	F(1,174)=0.63 P=0.430	F(1,133)=9.13 P=0.003	PT: MPH < PLAC; MPH: PT < DT; PLAC: PT > DT
TST	F(2,237)=2.41 P=0.092	F(1,157)=5.29 P=0.023	F(2,237)=1.57 P=0.210				PT: MPH > PLAC; MPH: PT > BL
TST + covariates	F(2,235)=2.63 P=0.074	F(1,161)=5.76 P=0.018	F(2,235)=1.94 P=0.174	F(1,222)=0.47 P=0.493	F(1,192)=4.44 P=0.036	F(1,157)=3.59 P=0.060	PT: MPH > PLAC; MPH: PT > BL
TIB	F(2,254)=1.27 P=0.282	F(1,128)=0.38 P=0.541	F(2,255)=1.46 P=0.234				
TIB + covariates	F(2,252)=1.65 P=0.194	F(1,131)=0.15 P=0.697	F(2,253)=1.61 P=0.202	F(1,232)=1.24 P=0.266	F(1,187)=0.84 P=0.362	F(1,128)=3.81 P=0.053	
WASO	F(2,288)=0.13 P=0.882	F(1,114)=2.76 P=0.099	F(2,291)=2.22 P=0.110				
WASO + covariates	F(2,278)=0.06 P=0.940	F(1,116)=4.04 P=0.047	F(2,281)=2.95 P=0.053	F(1,257)=1.16 P=0.283	F(1,195)=0.18 P=0.676	F(1,114)=7.38 P=0.008	
SST	F(2,272)=2.15 P=0.118	F(1,104)=10.07 P=0.002	F(2,275)=1.13 P=0.324				PT: MPH < PLAC; PLAC: PT < DT
SST + covariates	F(2,257)=3.12 P=0.046			F(1,236)=28.69 P<0.001	F(1,177)=1.06 P=0.304	F(1,104)=0.23 P=0.635	PT: MPH < PLAC; PLAC: PT < DT
SST-SUBJ	F(2,240)=1.31 P=0.271	F(1,128)=1.99 P=0.160	F(2,242)=2.25 P=0.107				
SST-SUBJ + covariates	F(2,240)=1.25 P=0.289	F(1,129)=1.61 P=0.207	F(2,241)=2.17 P=0.117	F(1,221)=0.75 P=0.386	F(1,180)=1.39 P=0.239	F(1,128)=0.63 P=0.428	
Wake time	F(2,261)=1.69 P=0.186	F(1,133)=8.02 P=0.005	F(2,263)=3.91 P=0.021				BL: MPH < PLAC; PT: MPH < PLAC; MPH: DT > BL
Wake time + covariates	F(2,250)=2.82 P=0.061	F(1,141)=6.33 P=0.013	F(2,252)=3.21 P=0.042	F(1,233)=46.11 P<0.001	F(1,190)=1.02 P=0.315	F(1,137)=1.24 P=0.268	BL: MPH < PLAC; PT: MPH < PLAC; PLAC: PT > DT
Wake-SUBJ	F(2,273)=1,48 P=0.230	F(1,119)=11.76 P=0.001	F(2,275)=2.46 P=0.087				BL: MPH < PLAC; PT: MPH < PLAC
Wake-SUBJ + covariates	F(2,256)=2.68 P=0.070	F(1,124)=10.57 P=0.001	F(2,259)=3.01 P=0.051	F(1,237)=45.46 P<0.001	F(1,186)=0.61 P=0.437	F(1,121)=0.29 P=0.590	BL: MPH < PLAC; PT: MPH < PLAC; PLAC: PT > DT
WBnumber	F(2,284)=0.73 P=0.483	F(1,117)=1.08 P=0.302	F(2,286)=0.82 P=0.443				

Abbreviations: BL, baseline; DT, during treatment; MPH, methylphenidate; PLAC, placebo; PT, post-treatment

Supplementary Table II (continued).

Variable	Interaction effect Time * Treatment	Main effects Treatment	Time	Holiday	RLS	Melatonin	Significant post-hoc effects[A]
WBnumber + covariates	F(2,282)=0.75 P=0.472	F(1,118)=1.01 P=0.317	F(2,284)=0.80 P=0.450	F(1,261)=0.01 P=0.929	F(1,198)=1.29 P=0.257	F(1,115)=0.38 P=0.541	
WBmean	F(2,263)=0.58 P=0.559	F(1,122)=1.12 P=0.291	F(1,265)=2.64 P=0.073				
WBmean + covariates	F(2,246)=0.93 P=0.396	F(1,127)=2.23 P=0.138	F(2,248)=3.69 P=0.026	F(1,227)=1.96 P=0.163	F(1,182)=0.89 P=0.347	F(1,124)=15.4 P<0.001	PT: MPH < PLAC; MPH: PT < BL
IV	F(2,82)=0.14 P=0.866	F(1,56)=3.85 P=0.055	F(1,81)=0.38 P=0.384				
IV + covariates	F(2,84)=0.32 P=0.728	F(1,59)=3.90 P=0.053	F(2,84)=0.44 P=0.647	F(1,113)=12.13 P=0.001	F(1,114)=2.45 P=0.120	F(1,54)=9.29 P=0.004	
AMP	F(2,91)=0.07 P=0.935	F(1,59)=0.26 P=0.612	F(2,91)=1.21 P=0.303				
AMP + covariates	F(2,90)=0.06 P=0.941	F(1,59)=0.05 P=0.823	F(2,90)=2.20 P=0.116	F(1,111)=10.76 P=0.001	F(1,98)=0.90 P=0.345	F(1,54)=1.05 P=0.310	
IS	F(2,85)=0.10 P=0.905	F(1,55)=0.11 P=0.746	F(2,84)=0.29 P=0.752				
IS + covariates	F(2,85)=0.22 P=0.801	F(1,55)=0.01 P=0.930	F(2,85)=0.55 P=0.582	F(1,114)=6.38 P=0.013	F(1,102)=2.44 P=0.122	F(1,49)=1.21 P=0.277	
M10	F(2,87)=0.13 P=0.879	F(1,56)=0.001 P=0.971	F(2,87)=0.36 P=0.697				
M10 + covariates	F(2,84)=0.17 P=0.844	F(1,55)=0.14 P=0.706	F(2,84)=0.80 P=0.455	F(1,114)=7.63 P=0.007	F(1,104)=1.34 P=0.250	F(1,50)=0.12 P=0.731	
M10 onset	F(2,83)=0.33 P=0.718	F(1,49)=1.28 P=0.264	F(2,81)=3.50 P=0.035				
M10 onset + covariates	F(2,79)=0.53 P=0.593	F(1,52)=0.49 P=0.486	F(2,78)=6.21 P=0.003	F(1,113)=15.90 P<0.001	F(1,113)=0.05 P=0.829	F(1,48)=0.62 P=0.435	PLAC: BL > DT; PLAC: PT > DT
L5	F(2,71)=0.99 P=0.377	F(1,48)=0.81 P=0.373	F(2,70)=4.13 P=0.020				MPH: BL > DT
L5 + covariates	F(2,70)=0.86 P=0.430	F(1,49)=0.98 P=0.327	F(2,71)=4.47 P=0.015	F(1,87)=0.53 P=0.469	F(1,99)=0.004 P=0.951	F(1,46)=1.30 P=0.261	MPH: BL > DT
L5 onset	F(2,88)=0.81 P=0.449	F(1,58)=0.04 P=0.837	F(2,86)=0.25 P=0.779				
L5 onset + covariates	F(2,87)=0.78 P=0.461	F(1,60)=0.12 P=0.730	F(2,87)=0.31 P=0.733	F(1,115)=1.36 P=0.245	F(1,109)=0.05 P=0.828	F(1,55)=0.08 P=0.775	

Abbreviations: BL, baseline; DT, during treatment; MPH, methylphenidate; PLAC, placebo; PT, post-treatment

Supplementary Table III. Linear mixed model results for the subjective sleep questionnaires

	Interaction effect	Main effects		Significant post-hoc effects[A]
Variable	**Time * Treatment**	**Treatment**	**Time**	
ELIT mood	F(2,91)=0.08 P=0.923	F(1,51)=0.19 P=0.663	F(2,90)=2.14 P=.123	
ELIT sleep	F(2,93)=1.01 P=0.369	F(1,54)=0.471 P=0.496	F(2,93)=7.54 P=0.001	BL > DT > PT
ELIT wake	F(2,92)=2.04 P=0.135	F(1,53)=0.07 P=0.797	F(2,92)=4.07 P=0.020	BL > PT
ESS	F(2,87)=0.08 P=0.920	F(1,49)=5.21 P=0.027	F(2,87)=1.57 P=0.214	PLAC > MPH

Abbreviations: BL, baseline; DT, during treatment; MPH, methylphenidate; PLAC, placebo; PT, post-treatment

[A] Sidak post-hoc test P<0.05

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