Hyperactive Night and Day? Actigraphy Studies in Adult ADHD: a Baseline Comparison and the Effect of Methylphenidate

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Study Objectives: To investigate parameters of sleep, activity, and circadian rhythm, as well as the effects of methylphenidate on these variables, in adults with ADHD.

Design: 1) Baseline group comparison; 2) Double blind, placebo-controlled, cross-over medication trial.

Setting: Data collection took place during daily lives of participants.

Participants: 39 normal controls and 33 adults with ADHD for baseline comparisons; 31 adults with ADHD in medication trial.

Interventions: Treatment with placebo and methylphenidate during medication trial.

Measurements and Results: Actigraphy and sleep log data were collected for 7 consecutive nights and days to obtain baseline values for ADHD and normal controls. Repeated measurements during placebo and methylphenidate treatment were conducted for the ADHD group.

Actigraphic sleep estimates showed that ADHD subjects took longer to fall asleep, had lower sleep efficiency, and had shorter within-night periods of uninterrupted sleep. These findings were consistent with subjective complaints. Actigraphic measures of ADHD subjects showed continuously elevated daytime activity levels, resulting in a 24-hour pattern that was more stable and less variable than in controls. Methylphenidate led to a later bedtime, later sleep onset, and reduction in sleep duration. However, number and total duration of nocturnal awakenings decreased, while mean duration of within-night periods of uninterrupted sleep increased, indicating more consolidated sleep.

Conclusions: Our data suggest that sleep problems are inherent in adults with ADHD and that methylphenidate reduced total sleep time but improved sleep quality by consolidating sleep.

Keywords: Adult ADHD, actigraphy, sleep, circadian rhythms, methylphenidate

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INTRODUCTION

ACTIGRAPHS ARE SMALL DEVICES, USUALLY WORN AROUND THE WRIST, THAT DETECT AND STORE MOVEMENT FOR LATER ANALYSIS OF LEVELS OF ACTIVITY, sleep and wake parameters, and circadian rhythm parameters.[1] These measurement goals make actigraphy a useful tool for objectively studying attention deficit hyperactivity disorder (ADHD), since this disorder is by definition associated with hyperactivity and with sleep problems.[2] Actigraphy has indeed been utilized in studying children with ADHD, but it has rarely been employed in adults with the disorder. We therefore conducted an extensive actigraphy study of daytime and nighttime activity, sleep/wake parameters, and circadian rhythms in adults carefully diagnosed with ADHD; we also collected data to measure the effects of stimulant medication. We gathered these data to provide tentative answers to the 4 research questions described below.

1) Are adults with ADHD more active (as measured by actigraphs) during the day and/or during the night than normal controls? Children with ADHD show higher levels of daytime activity than normal controls.[3] We know of only one study that used daytime actigraphy in an adult population suspected of childhood ADHD. The patient group in this study could be distinguished from normal controls by higher activity counts from the actigraphs.[4] However, the patient group in this study was primarily classified as "Antisocial Violent Offenders," thus our study is the first to explore daytime activity in adult participants with a primary diagnosis of ADHD.

With respect to nighttime activity, Cohen-Zion and Ancoli-Israel discussed 4 studies that utilized actigraphs in a child ADHD sample and they reported that the evidence was inconclusive, although most studies reported more nighttime activity and increased nighttime variability in activity levels.[5] Two studies have used actigraphy to evaluate nocturnal activity in an adult ADHD population; in one study the ADHD group showed higher mean activity levels than normal controls,[6] whereas the other study reported no difference.[7] Both studies reported a higher movement index (percentage of epochs with an activity count > 0) during the night.

2) Are there differences in actigraphic sleep parameters between adults with and without ADHD? Problems with sleep are frequently reported in children with ADHD.[2] In particular, parental reports of sleep problems in children with the disorder are highly prevalent, although results of more objective measurements of sleep (e.g., polysomnography) are equivocal; there does not seem to be one specific disturbance of sleep architecture relat-

Disclosure Statement

This is not an industry supported study. Dr. Kooji is a consultant to and on the speakers' bureau of Eli Lilly and Company and Janssen-Cilag Ltd. Dr. Buitelaar has participated in speaking engagements for Eli Lilly and Company , Janssen-Cilag Ltd., and Medice and is a consultant for Eli Lilly and Company, Janssen-Cilag Ltd, and Bristol-Myers Squibb. Drs. Boonstra, Oosterlaan, Sergeant, and Van Someren have indicated no conflicts of interest.

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ed to the disorder. ADHD has also been associated with a higher prevalence of sleep disorders like periodic limb movement[8] and sleep disordered breathing.[9] It has even been suggested that sleep problems in children with ADHD may be the primary condition that results in secondary symptoms of hyperactivity and inattention, rather than ADHD being the primary condition associated with specific sleep problems.[5]

Several studies have indicated that sleep disorders in adults may also be misdiagnosed as ADHD.[10] In adult men with antisocial personality disorders, Lindberg et al. found a strong positive correlation between childhood ADHD scores and abnormal sleep architecture (increased percentage of stage 4 sleep) as measured by polysomography.[11] Kass et al. also established a relation between scores on an adult ADHD questionnaire and scores on several sleep problem questionnaires (specific sleep problems were not mentioned in this study).[12] We know of no direct studies of sleep characteristics of adults carefully diagnosed with ADHD.

3) Are there differences in circadian rhythm parameters between adults with ADHD and normal controls? Actigraphy also yields information on the amplitude, phase, and stability of the circadian (24-hour) pattern of activity, which may reflect functionality of the hypothalamic suprachiasmatic nucleus, the biological clock of the brain. There is little research into circadian rhythms in ADHD. Van der Heijden et al. established that the nocturnal onset of melatonin secretion was delayed in children with ADHD.[2] The authors suggested that the chronic sleep onset insomnia often encountered in children with ADHD may be a delayed sleep phase circadian rhythm disorder.

4) What are the effects of treatment with methylphenidate on the above-mentioned activity, sleep, and circadian rhythm parameters in adults with ADHD? Methylphenidate (Mph) has been the preferential treatment for ADHD for decades, both for children and adults.[13,14] Very few studies have investigated the effects of this stimulant on hyperactivity by means of actigraphy, but the few available outcomes indicated a decrease in activity during the day with treatment in children with ADHD.[15] We know of no daytime medication effect studies in the adult ADHD population, but the one available actigraphy treatment study reporting effects of stimulants during the day (last dose at 16:00) showed a decrease of nighttime activity level with medication in comparison to placebo.[6] Daytime activity data were not reported.

Insomnia is a frequent side effect of stimulant medication.[16] Other sleep disturbances, like tossing or moving and shorter sleep time, have also been indicated as side effects of stimulant treatment.[17] Some researchers have suggested that sleep problems may represent features of the behavioral phenotype of ADHD rather than adverse side effects of medication.[18] Actigraphy studies on the effects of stimulants on sleep in children with ADHD have noted differences in total sleep time, which decreased with medication.[19] Actigraphic studies of medication in adults are not available.

METHODS

Participants

ADHD participants

We included data of 33 adults with ADHD, 16 men and 17 women (we strove for inclusion of equal number of each sex). The average age was 37.9 years (SD 10.3), and the average IQ was 104.1 (SD 18.5). One of the participants was diagnosed with ADHD hyperactive / impulsive subtype, the other 32 were diagnosed with ADHD combined subtype. Thirty-one of these participants entered the medication trial after a baseline comparison. One female participant had to be excluded from the medication trial due to use of a weight control supplement that contained a stimulating substance (ephedra), and one male participant was excluded because of a positive opiate urine screening during the first week of the trial.

The average age for the 31 participants of the medication trial was 37.8 (SD 10.6), the average IQ was 104.1 (SD 18.2). None of the participants had been treated with methylphenidate (Mph) prior to this study. The participants were self-referred or referred by other clinicians for assessment of ADHD to an outpatient clinic in the Netherlands. Details of the diagnostic procedure and the instruments used have been provided elsewhere.[14,20] In brief, participants underwent a standardized clinical assessment by a psychiatrist. In addition to a semi-structured clinical diagnostic interview for ADHD and comorbid disorders, including sleep complaints, several structured interviews and questionnaires were used to assess ADHD and comorbid psychiatric disorders. To be given a diagnosis of adult ADHD, subjects had to (1) currently meet at least 5 of 9 DSM-4 criteria of inattention and / or at least 5 of 9 DSM-4 criteria of hyperactivity / impulsivity (this cutoff point is in line with previous research[21]); (2) meet at least 6 of 9 DSM-4 criteria of inattention and / or at least 6 of 9 DSM-4 criteria of hyperactivity / impulsivity in childhood; (3) describe a persistent course of ADHD symptoms from childhood to adulthood; and (4) endorse a moderate to severe level of impairment attributed to ADHD symptoms.

Normal Control Participants

Thirty-nine normal control (NC) participants, 18 men and 21 women, participated in the baseline comparison study. The average age was 37.8 years (SD 9.5), and the average IQ was 109.3 (SD 15.4). Controls were matched to ADHD participants by age and sex on group level. We only included NCs that did not a) show any evidence of ADHD or other psychiatric diagnoses, b) use any drugs or psychotropic medications, c) consume more alcohol than considered safe by official Dutch guidelines, d) ever receive a psychiatric diagnosis (including substance abuse), or e) seek help for mental health problems (including burnout) during the last 3 years. IQ as estimated with a short version of the Wechsler Adult Intelligence Scale-3 had to be above 75.

The local Medical Ethical Committee approved the study, and all subjects completed a written informed consent form before inclusion in the study.

Procedure

All participants wore the actigraph for 7 consecutive nights and days to obtain baseline values. The ADHD participants then entered a double-blind, placebo-controlled, cross-over trial of Mph. The design of this trial and clinical outcomes are described in detail elsewhere.[14,20] In brief, there were two 3-week treatment periods for each participant, one period of 3 weeks for Mph and one period of 3 weeks for placebo, with 1 week of washout in between. The order of treatment (Mph-placebo or placebo-Mph)

was randomized. Study medication was titrated from low to high doses to avoid exposure to high initial doses of active medication and to minimize side effects. Participants started with 0.5 mg/kg/d in week 1, followed by 0.75 mg/kg/d in week 2, and up to 1.0 mg/kg/d in week 3, unless adverse effects emerged. Medication was dosed 4 or 5 times daily (depending on rebound effects). The last dose was always prescribed at 20:00. Subjects used a device (Memos) containing compartments for tablets and a timer in order to take the medication on time. Compliance was monitored by electronic registration of the opening of the device at each visit to the pharmacy. Compliance was defined as opening the device within 15 min of the timer's signal > 80% of the time. Repeated measurements with the actigraphs took place during week 3 (highest dose of Mph, or placebo) and during week 7 (highest dose of Mph, or placebo). All recordings were obtained between July 2000 and February 2003.

Materials

Actigraphy

We used the Actiwatch Activity Monitoring System, developed by Cambridge Neurotechnology. We set our epoch length to 1 min, in accordance with the 2002 Practice Parameters for the use of actigraphy.[22] Epoch length refers to the period of time the Actiwatch accumulates activity data before saving the sampling and resetting the counter to zero. We instructed participants to wear the Actiwatch on the non-dominant wrist, as recommended by Littner et al.[22]

Table 1—Description of objective actigraphy and associated subjective sleep parameters (first 3 parameters).

Parameter	Description
Bedtime (hr)	as noted by participant in log
Get up time (hr)	as noted by participant in log
Time in bed (hrs)	difference between get up time and bedtime
Sleep start (hr)	as estimated from actigraph data
Sleep end (hr)	as estimated from actigraph data
Assumed sleep time (hrs)	difference between sleep end and sleep start
Actual sleep time (hrs)	assumed sleep time minus periods of wakefulness during the night
Actual sleep %	percentage of sleep between sleep start and sleep end
Wake bouts (number of)	number of times participant wakes up during sleep
Actual wake time (hrs)	hours of wakefulness during assumed sleep time
Actual wake %	percentage of wakefulness during assumed sleep time
Sleep efficiency	percentage of sleep between bedtime and sleep end
Sleep onset latency (hrs)	the time it takes from bedtime to sleep start
Sleep bout duration (hrs)	average length of uninterrupted sleep between two consecutive awakenings
Wake bout duration (hrs)	mean duration of periods of wakefulness

Calculation of Actigraphic Sleep Variables

Objective estimates of sleep were calculated from the actigraphy recordings using the Actiwatch Sleep Analysis software (version 1.19, 2001, Cambridge Neurotechnology, Cambridge, UK). The Actiwatch and accompanying software compare favorably to other such packages in reliably recording activity[23] and estimating sleep.[24] The patterning of periods of rest and activity during the night is correlated — but not identical — to periods of sleep and wakefulness: estimates are useful though,[25] and will be referred to as "sleep" and "wakefulness" throughout this paper. We obtained the objective sleep variables described in Table 1 for each subject at each condition by averaging over the recorded nights.

Since sleep is not a continuous process, the actual sleep time is usually lower than the time spent in bed. The mean sleep and wake bout duration give an impression of the structure of sleep. The sleep bout duration measures the average length of uninterrupted sleep between 2 consecutive awakenings. Sleep bouts of long duration are related to high sleep efficiency, the occurrence of "deep," i.e., slow wave sleep, and are negatively related to nocturnal awakenings.[26] The wake bout duration provides another indication of sleep depth and continuity; long arousals are more disruptive to sleep than very brief ones.

Calculation of Actigraphic Circadian Sleep-Wake Rhythm Variables

Activity during the major sleep period and the patterning of rest and activity over days and nights may provide useful information. We calculated a number of nonparametric circadian rhythm variables, which compare favorably to other methods for rhythm quantification, including cosine fitting, complex demodulation, the Lomb-Scargle periodogram and autoregression.[27] The *interdaily stability* (IS) quantifies the strength of coupling of the sleep-wake rhythm to the 24-hour regularity in the environment. A low IS is indicative of a weak circadian rhythm. The *intradaily variability* (IV) quantifies the fragmentation of periods of rest and activity. A high IV is indicative of many transitions between periods of rest and activity. For details on calculation of these variables, the reader is referred to our previous work.[23,27-29] A measure indicating the activity level during the major sleep period is L5, defined as the mean activity level during the sequence of the 5 least active hours in the 24-hour average activity profile. L5 provides an indication of restfulness and regularity of sleep periods with lower values indicating a more regular "core" sleep period. L5-Onset indicates the clock hour at which this major restful phase commences. A measure indicating the activity level during the major wake period is M10, defined as the sequence of the 10 most active hours in the 24-hour average activity profile. M10 provides an indication of how active and regular the major wakefulness periods are. M10-Onset indicates the clock hour at which this major active phase commences. Finally, the *relative_amplitude* (RA) quantifies the difference between daytime (M10) and nighttime (L5) activity levels. A low RA indicates little difference between activity levels during the major rest and activity phases and/or extreme irregularity; both of these are indicative of a weak circadian rhythm.

Sleep and Activity Log

In accordance with the 2002 Practice Parameters for the use of actigraphy,[22] we asked participants to complete a sleep and ac-

Table 2—Occupation of ADHD participants and normal controls.

Occupation Category	Percentage of group	
	ADHD	Controls
unknown occupation	6.1	12.8
management occupation	12.1	15.4
business & financial operations occupation	3.0	12.8
computer & mathematical occupation	6.1	0.0
community & social services occupation	3.0	2.6
education, training, & library occupation	12.1	2.6
arts, design, entertainment, sports, & media occupation	6.1	2.6
healthcare practitioners & technical healthcare occupation	18.2	20.5
healthcare support occupation	3.0	0.0
food preparation & serving related occupation	0.0	5.1
protective service occupation	3.0	0.0
personal care & service occupation	3.0	0.0
sales & related occupation	6.1	5.1
office & administrative support occupation	12.1	17.9
construction & extraction occupation	6.1	0.0
transportation & material moving occupation	0.0	2.6

tivity log twice a day (morning and evening) for each day they wore the actigraph. The log contained questions about subjective experience of different aspects of sleep, rated on a 5-point Likert scale (e.g., "How well rested did you feel today?", "How well did you sleep?"). High scores indicated poor subjective experience. The log also contained questions about activities during the day, use of medication, alcohol, caffeinated beverages, cigarettes, and bed- and wake times. In the log, participants noted periods they did not wear the actigraph, due to showering and other water-related activities. These periods of time were manually discarded from the data before analysis.

Statistical Approach

Since it has been noted previously that sleep-wake rhythms may differ with age, sex, and season,[30] and since we obtained data throughout the year, it was desirable to include these factors as covariates. Season is a circular variable, which has previously successfully been linearized into 2 variables: day length and rate of change in day length.[23,28] In a repeated measures design, however, these season variables are time-varying covariates. A solution was found in the application of hierarchical regression analysis (i.e., random coefficient analysis) to account for the interdependency of the data points inherent to the hierarchical structure of the design, i.e. sequential observations within subjects (MLwiN software, Centre for Multilevel Modelling, Institute of Education, London, UK).[31] Although not strictly necessary, we consistently applied this method to first investigate differences between baseline assessments of ADHD participants and control subjects.

For all variables mentioned above we obtained effect estimates from the following regression equation:

$$Outcome\_Variable_j = ß_{0j} + ß_{1j}*ADHD + ß_{2j}*Male + ß_{3j}*Age + ß_{4j}*Daylength + ß_{5j}*DaylengthChange \quad (1)$$

where $ß_{0j} – ß_{5j}$ are the effect estimates for the intercept, the effect of ADHD, sex, age and season, optimized to fit the observations of all j subjects.

We subsequently investigated the effect of Mph in the ADHD participants on the same variables. For all variables we obtained effect estimates from the following regression equation:

$$Outcome\_Variable_{ij} = ß_{0j} + ß_{1ij}*Mph + ß_{2ij}*Male + ß_{3ij}*Age + ß_{4ij}*Daylength + ß_{5ij}*DaylengthChange + ß_{6ij}*Placebo + ß_{7ij}*Time \quad (2)$$

where $ß_0 – ß_7$ are the effect estimates for the intercept, the effect of Mph, sex, age, season, placebo, and time in study (whether methylphenidate was taken during the first or second period of the trial), as optimized to fit all i observations of all j subjects.

Effect estimates with two-tailed Wald–statistic P-values < 0.05 were regarded as significant; non-significant terms were excluded from the regression equation and a next iteration of fitting the resulting sparser equation commenced.

RESULTS

Baseline comparisons

Independent-samples *t*-tests demonstrated that there were no differences between the 2 groups in age ($t_{1,70} = 0.04$, P = 0.97) or IQ ($t_{1,70} = -1.31$, P = 0.19).

Since daily activities influence actigraphy parameters, we compared the ADHD and NC groups with respect to occupation. Table 2 presents the occupation of participants, coded according to the Standard Occupational System (U.S. Department of Labor, Bureau of Labor Statistics). We also coded occupation according to physical load of the activities (e.g., none, light, medium, heavy, and unknown). A 2 (ADHD versus NC) by 5 (physical load code) contingency tables analysis indicated no differences in distribution of physical load between the two groups [Pearson's χ^2 (4, N = 72) = 4.67, P = 0.32, Cramer's V = 0.26]. None of the participants worked nightshifts.

Table 3 presents the grand means and standard errors for all variables at baseline and after treatment with Mph (the numbers provided are raw data). The effect estimates of the variables finally included in the regression analysis for the baseline group comparisons are shown in Table 4, providing information on which factors influenced the final outcomes. An example of how to interpret Table 4 and Table 5 is provided in a note following Table 4.

As can be expected for ADHD, the daytime *activity* level M10 was 52 counts (17%) higher in the ADHD group than in control subjects. No differences were found in nighttime activity levels.

After having accounted for the variance due to age, sex, and season, the actigraphic *sleep* variables indicated less sound sleep in the ADHD group. Compared to NCs, ADHD participants showed a 3.5% lower sleep efficiency, a 6-min (67%) longer sleep onset latency, and a 6-min (34%) shorter average sleep bout duration uninterrupted by wakefulness.

The *circadian* variables, on the other hand, did not indicate disturbances of circadian organization of the sleep-wake cycle. On the contrary, compared to NCs, participants with ADHD showed 0.07 points (13%) increase in IS and 0.13 points (16%) decrease in IV, respectively, indicative of a more repeatable daily schedule of activities and more consolidated periods of rest and activity.

The *subjective* variables indicated that ADHD participants felt less well-rested in general (0.82 or 36%) as well as directly after waking up (0.72 or 30%), and that they rated their sleep quality lower (0.61 or 31%) than control subjects. This is consistent with the objectively lower sleep efficiency than normal subjects.

Table 3—Means and standard errors of the subjective and objective variables in control subjects and ADHD subjects (first 2 columns of data). The rightmost 2 columns of data give means and standard errors of the variables after placebo versus Mph treatment.

	Group/Assessment			
	Baseline		ADHD Treatment	
	Controls	ADHD	Placebo	Methylphenidate
Variable (unit of measurement)				
Subjective variables				
Well-rested (a.u.)	2.26±0.08	3.07±0.13[c]	2.84±0.15	3.03±0.14
Sleep onset latency (hrs)	0:12±0:01	0:20±0:04[a]	0:17±0:03	0:24±0:04
Difficulty initiating sleep (a.u.)	1.66±0.10	2.29±0.19[b]	2.15±0.19	2.33±0.19
Nocturnal awakenings (a.u.)	1.02±0.12	1.34±0.17	0.99±0.16	0.82±0.14[b]
Sleep quality (a.u.)	1.97±0.06	2.56±0.13[c]	2.47±0.14	2.67±0.13
Rested at wake up (a.u.)	2.41±0.08	3.12±0.12[c]	3.01±0.14	3.12±0.13
Sleep variables				
Bedtime (hr)	00:23±00:07	00:16±00:08	00:14±00:59	00:34±01:03[b]
Get up time (hr)	08:24±00:09	08:18±00:10	08:15±00:55	08:12±01:02
Time in bed (hrs)	8:01±0:07	8:01±0:09	8:00±0:53	7:38±1:03[b]
Sleep start (hr)	00:33±00:07	00:30±00:08	00:30±00:59	00:55±01:01[c]
Sleep end (hr)	08:20±00:09	8:11±00:09	8:08±00:55	08:06±01:01
Assumed sleep time (hr)	7:47±0:07	7:40±0:08	7:37±0:50	7:11±0:56[c]
Actual sleep time (hrs)	6:53±0:06	6:45±0:07	6:44±0:44	6:23±0:42[c]
Actual sleep % (%)	89±1	88±1	88±4	89±4[a]
Actual wake time (hrs)	0:53±0:03	0:55±0:03	0:53±0:21	0:47±0:25[a]
Actual wake % (%)	11±1	12±1	12±4	11±4[a]
Sleep efficiency (%)	86±1	84±1[b]	84±5	86±6
Sleep onset latency (hrs)	0:10±0:01	0:14±0:01[c]	0:15±0:11	0:20±0:16[a]
Wake bouts (#)	28±1	27±1	27±8	23±9[c]
Sleep bout duration (hrs)	0:19±0:02	0:16±0:00[a]	0:16±0:04	0:20±0:07[c]
Wake bout duration (hrs)	0:01±0:00	0:02±0:00	0:02±0:00	0:02±0:00
Circadian variables				
IS	0.51±0.02	0.57±0.02[b]	0.56±0.02	0.55±0.02
IV	0.81±0.03	0.69±0.03[b]	0.72±0.03	0.77±0.03[a]
L5	16±2	16±1	15±2	13±1
M10	303±17	353±17[a]	341±15	325±19
RA	0.90±0.01	0.91±0.01	0.91±0.01	0.01±0.01
L5 Onset	01:46±00:09	01:33±00:09	01:34±00:12	01:51±00:10[a]
M10 Onset	09:49±00:14	09:58±00:17	09:58±00:18	10:03±00:19

[a] = $p<0.05$, [b] = $p<0.01$, [c] = $p<0.001$

A.u. = arbitrary units; hr = clock time; hrs = hours (duration); IS = interdaily stability; IV = intradaily variability; L5 = the least active 5-hour period of the average activity profile; M10 = the most active 10-hour period of the average activity profile; RA = relative amplitude

ADHD participants showed an 8-minute (65%) longer subjective sleep onset latency and 0.60 points (36%) more difficulty falling asleep. These findings are consistent with the objectively increased sleep latency of 6 minutes.

Medication Comparisons

The mean weight of the ADHD participants was 77.5 kg (SD = 12.8). The mean dose of Mph administered in the 3rd week of the medication phase of the trial was 0.94 mg/kg/day (SD = 0.15). Twenty of 28 participants (64.5%) were compliant, according to the definition in the Methods section. The other 8 opened their Memos device outside the 15-min limit. Compliance data were missing for 3 participants.

The clinical effects of treatment with Mph in this sample have been described earlier.[14] In brief, the response rate of Mph varied between 38% and 51%, and using placebo between 7% and 18%, depending on outcome measure used. Side effects were reported in 82% of the group with Mph, compared to 69% with placebo. Sleeping problems were reported in 33% of the cases with Mph, compared to 22% with placebo.

Table 5 shows the effect of Mph and the covariates age, sex, and season resulting from the regression analyses. Neither placebo treatment nor time in study affected any of the variables, and therefore, these factors were not included in the table.

There was no change in *activity* level during the day (M10) with medication. The actigraphic *sleep* variables indicated that Mph is associated with delays in bedtime (19 min), sleep onset latency (5 min or 34%) and sleep start (24 min). Consequently, the assumed sleep time was reduced by 25 min (6%) and the actual sleep time by 20 min (5%). However, during this shorter sleep period, sleep appeared to be more consolidated as indicated by a decrease in the number of nocturnal awakenings (-3.8 or 14%), a lower percentage of wakefulness (-0.9 or 8%), and a 3-min (21%) increased average duration of uninterrupted sleep bouts.

The *circadian* variables showed that treatment delayed the onset of the 5 least active hours (L5) by 18 min, in accordance with the delayed bedtime and sleep start reported above. Treatment increased the fragmentation of periods of rest and activity (IV) by 0.07, or 9%.

Table 4—Regression parameter estimates (± standard error) of the subjective and objective variables comparing control subjects and ADHD subjects and effects of sex, age, and season over all subjects in both groups.

	Regression Model					
	Intercept	**ADHD**	**Male**	**Age**	**Daylength**	**Daylength Change**
Variable (unit of measurement)						
Subjective variables						
Well-rested (a.u.)	2.43±0.12	0.82±0.14[c]	-0.37±0.14[b]			
Sleep onset latency (hrs)	0:12±0:02	0:08±0:04[a]				
Difficulty initiating sleep (a.u.)	1.67±0.13	0.60±0.19[b]				0.52±0.26[a]
Nocturnal awakenings (a.u.)	1.17±0.10					
Sleep quality (a.u.)	2.10±0.10	0.61±0.13[c]	-0.29±0.13[a]			
Rested at wake up (a.u.)	2.58±0.11	0.72±0.13[c]	-0.37±0.13			
Sleep variables						
Bedtime (hr)	0:05±0:06		0:33±0:09[c]			0:34±0:13[b]
Get up time (hr)	9:16±0:24			-0:01:25±0:00:37[a]		
Time in bed (hrs)	8:59±0:20			-0:01:30±0:00:31[b]		
Sleep start (hr)	0:16±0:06		0:34±0:09[c]			0:30±0:13[a]
Sleep end (hr)	9:11±0:23			-0:01:24±0:00:36[a]		
Assumed sleep time (hr)	8:36±0:18		-0:21±0:10[a]	-0:01:06±0:00:29[a]		
Actual sleep time (hrs)						
7:04±0:06		-0:29±0:09[b]				
Actual sleep % (%)	85±2				0.4±0.2[a]	
Actual wake time (hrs)	1:15±0:10				-0:01±0:00[a]	
Actual wake % (%)	16±2				-0.4±0.2[a]	
Sleep efficiency (%)	80±2	-3.5±1.1[b]			0.6±0.2[b]	
Sleep onset latency (hrs)	0:23±0:04	0:06±0:02[c]		-0:00:11±0:00:05[a]	-0:00:45±0:00:21[a]	-0:05±0:02[a]
Wake bouts (#)	46±5			-0.3±0.1b	-0.7±0.3[a]	
Sleep bout duration (hrs)	0:06±0:04	-0:06±0:02[a]			0:01±0:00[b]	
Wake bout duration (hrs)	0:01±0:00					
Circadian variables						
IS	0.51±0.02	0.07±0.02[b]				
IV	0.81±0.03	-0.13±0.04[b]				
L5	23±5		5±2[a]	-0.2±0.1[a]		
M10	301±17	52±24[a]				
RA	0.96±0.03		-0.05±0.01[b]	0.002±0.001[a]		
L5 Onset	1:41±0:06					
M10 Onset	9:56±0:10					

[a] = P<0.05, [b] = P<0.01, [c] = P<0.001

A.u. = arbitrary units; hr = clock time; hrs = hours (duration); IS = interdaily stability; IV = intradaily variability; L5 = the least active 5-hour period of the average activity profile; M10 = the most active 10-hour period of the average activity profile; RA = relative amplitude. As an example of the interpretation of the regressions, consider the model estimate of sleep bout duration in an ADHD subject aged 30, as measured on August 13, when Daylength is 14.85 hours and DaylengthChange is -0.42 hrs/week. Filling out the intercept, variables and parameter estimates in the regression formula ($Outcome\_Variable_j = ß_{0j} + ß_{1j}$*ADHD + $ß_{2j}$*Male + $ß_{3j}$*Age + $ß_{4j}$*Daylength + $ß_{5j}$*DaylengthChange) yields the following outcome: Sleep bout duration (hrs) = 0:06 + (-0:06*1) + (0*1) + (0*30) + (00:01*14.85) + (0*-0.42) = 00:06 - 00:06 + 00:01 * 14.85) = 00:15 (rounded to fifteen minutes).

Subjectively, Mph reduced the nocturnal awakening rating by 0.36 or 31%, which is in agreement with the objective decrease in wake time and percentage.

As in previous observations, the covariates sex, age, and season accounted for a significant part of the variance in the sleep-wake rhythm. Although a full description of these effects is outside the scope of this paper, the most significant findings (P<0.001) will briefly be discussed here. With regard to sex differences, males went to bed more than a half-hour later than females in the overall analysis (including both control subjects and the baseline assessments of the ADHD subjects). With regard to age, in the ADHD group, sleep efficiency increased by 0.20% per year of age, the number of awakenings decreased by 0.4/y, and the duration of uninterrupted sleep bouts increased by 16 seconds/y of age. With regard to season, in the ADHD group, sleep end and get up time were advanced by 8 min for each hour increase in day-length, indicating an earlier awakening in the summer than the winter.

To explore the relationship between clinical improvement and improvement in sleep parameters with Mph, we calculated correlations between difference scores in several sleep parameters and clinical response as measured in Kooij et al.[14] Correlations were low, and none of them reached significance (data available from the first author).

Explorative Analyses of Comorbidity

To obtain a first indication of the influence of comorbid disorders on actigraphic parameters in the ADHD group, we calculated correlations between the actigraph parameters that showed sig-

Table 5—Regression parameter estimates (± standard error) of the subjective and objective variables comparing Mph treatment versus baseline and placebo in ADHD subjects. Regression models corrected for effects of sex, age, and season.

	Regression Model					
	Intercept	**Methylphenidate**	**Male**	**Age**	**Daylength**	**Daylength Change**
Variable (unit of measurement)						
Subjective variables						
Well-rested (a.u.)	3.20±0.14		-0.46±0.20[a]			
Sleep onset latency (hrs)	0:20±0:03					
Difficulty initiating sleep (a.u.)	2.25±0.15					
Nocturnal awakenings (a.u.)	1.14±0.14	-0.36±0.13[b]				
Sleep quality (a.u.)	2.56±0.11					
Rested at wake up (a.u.)	3.09±0.11					
Sleep variables						
Bedtime (hr)	0:14±0:10	0:19±0:06[b]				
Get up time (hr)	9:55±0:28				-0:08±0:02[c]	
Time in bed (hrs)	10:01±0:33	-0:20±0:07[b]	-0:31±0:14[a]	-0:01:22±0:00:39[a]	-0:04±0:02[a]	
Sleep start (hr)	0:30±0:09	0:24±0:07[c]				
Sleep end (hr)	9:44±0:27				-0:07±0:02[c]	
Assumed sleep time (hr)	8:42±0:27	-0:25±0:06[c]	-0:32±0:13[a]		-0:03±0:02[a]	
Actual sleep time (hrs)						
6:44±0:06	-0:20±0:06[c]					
Actual sleep % (%)	83±2	1±0[a]		0±0[a]		-2.8±1.2[a]
Actual wake time (hrs)	1:39±0:13	-0:05±0:02[a]		-0:00±0:00[a]	-0:01±0:00[a]	0:15±0:06[a]
Actual wake % (%)	17±2	-1±0[a]		0±0[a]		2.8±1.2[a]
Sleep efficiency (%)	77±2			0.20±0.06[c]		
Sleep onset latency (hrs)	0:33±0:06	0:05±0:02[a]		-0:00:29±0:00:09[b]		
Wake bouts (#)	42±4	-4±1[c]		-0.4±0.1[c]		4.3±2.1[a]
Sleep bout duration (hrs)	0:06±0:02	0:03±0:00[c]		0:00±0:00[c]		
Wake bout duration (hrs)	0:02±0:00					
Circadian variables						
IS	0.60±0.02		-0.07±0.03[b]			
IV	0.71±0.02	0.07±0.03[a]				
L5	15±1					
M10	381±13		-96±19[c]			
RA	0.91±0.01					
L5 Onset	1:33±0:09	0:18±0:07[a]				
M10 Onset	9:56±0:10					

[a] = P<0.05, [b] = P<0.01, [c] = P<0.001

A.u. = arbitrary units; hr = clock time; hrs = hours (duration); IS = interdaily stability; IV = intradaily variability; L5 = the least active 5-hour period of the average activity profile; M10 = the most active 10-hour period of the average activity profile; RA = relative amplitude

nificant differences in the baseline analyses and the participants' scores on the Hamilton Depression Scale and the Hamilton Anxiety Scale. These rating scales were part of the diagnostic procedure for ADHD and comorbidity. Depression and anxiety were selected because these disorders are known for their impact on sleep.[32,33] The correlations between the scales and the actigraphy parameters ranged between |.02| and |.27|. None of the correlations reached significance (data available form the first author).

Subjective Sleep Complaints

Subjective sleep complaints were questioned in the semi-structured clinical diagnostic interview. The most prominent findings were that two-thirds of the ADHD participants said they have always had difficulty sleeping (65%), and that trouble going to bed on time (87%) and difficulty getting out of bed (71%) were experienced by the vast majority of the participants, suggesting a phase-delayed sleep-wake cycle. Half of the subjects reported daytime sleepiness.

DISCUSSION

The present study provides some initial answers to questions concerning activity, sleep, and circadian rhythms, as measured with actigraphs and subjective reports in an adult ADHD population. To our knowledge, this study is the first to objectively establish increased daytime activity in adults with ADHD, which answers our *first* research question. Our results are consistent with studies conducted in the child ADHD population.[3] We did not find a difference in nighttime activity L5 between our ADHD participants and the NCs. This result deviates from what we would expect based on the literature on children with the disorder, in which it is suggested that one of the more consistent findings in this population is increased nighttime activity.[5] Data on adults with ADHD are equivocal, with one study[6] reporting more nighttime activity and the other[7] not. However, direct comparison with these studies is difficult since different dependent variables were reported. Moreover, sample size in both studies was small, so our data may prove more reliable. A possible explanation for the difference between children and adults could be found in the fact that adults

choose their own bedtime and daytime activities, which may lead to less activity during the night. It may also be that activity in the 5 least active hours of the average 24-hour rest-activity profile provides a view of activity during the *core* sleep period, but is not sensitive enough to quantify *whole-night* nocturnal activity, as is indeed suggested by the findings discussed below.

With respect to our *second* research question, our results indicate that there are indeed differences in actigraphic sleep parameters between adults with and without ADHD. Adults with ADHD show lower sleep efficiency, longer sleep onset latency, and shorter average duration of within-night uninterrupted sleep periods. In children with ADHD, actigraphy studies have shown mixed results, but longer sleep onset latencies have been reported frequently.[5]

Our *third* research question ("Are there differences in circadian rhythm between adults with ADHD and normal controls?") also leads to a positive answer, although this answer in part differs from what one would intuitively expect in this population. In the nonparametric circadian rhythm analyses, we found that participants with ADHD showed a more repeatable daily schedule of activities and more consolidated periods of rest and activity than the NCs. In children with ADHD, there have been some suggestions of deviant circadian patterns.[2]

The fact that our data do not point towards deviant circadian patterning in adults with the disorder may be related to some form of compensation of adults with ADHD. They may be trying to impose external structure to counterbalance their lack of internal structure, as has been reported to occur in healthy aging as well.[34] Alternatively, it may be that there was less difference in high and low activity levels in the ADHD group because their daytime activity was near maximal most of the time. Indeed, it has been previously found in demented elderly that interdaily stability and intradaily variability appear less disturbed if daytime activity levels are high.[23] Increased sleep onset latency and subjective complaints on getting to bed at night and getting up in the morning are suggestive of a delayed phase in the circadian organization of sleep and wakefulness, which is in agreement with a recently reported delayed melatonin onset phase in children with ADHD-related sleep-onset insomnia.[35] Future studies with different parameters (e.g., temperature, melatonin) should shed further light on circadian patterning in participants with ADHD: do they go to bed later because they are too restless to sleep or because they show a phase delay in their circadian rhythm?

Our *fourth* research question was "What are the effects of treatment with Mph on activity, sleep parameters, and circadian rhythm in adults with ADHD?" No effects of Mph on daytime or nighttime *activity level* were found in our placebo-controlled study, thus disproving the suggested trend towards decreased nocturnal activity with stimulant treatment in adult ADHD in one previous open-label study.[6] Our results agree with earlier studies on stimulant treatment in childhood ADHD, reporting no effect on nocturnal activity.[36]

As to the effect of Mph on *sleep* parameters, Mph induced a delay in bedtime and sleep start, and increased sleep onset latency. As a result, the sleep *duration* decreased. In agreement with our findings, child ADHD studies have reported longer sleep onset latency and shorter total sleep time as measured by actigraphy after stimulant treatment.[19,36] An interesting result in our study was improvement of sleep quality, as reflected by fewer nocturnal awakenings, and an increase in the average duration of within-night periods of uninterrupted sleep. In agreement with the objective sleep quality improvement, participants indicated that they woke up fewer times during the night with medication, as was also found in a previous study on the effects of stimulants on sleep in adult ADHD.[6] Our results are in part similar and in part contradictory to the results of Schwartz et al.,[19] where both quality and quantity of sleep deteriorated with medication. A possible explanation for our results can be found in the timing of the last dose of medication, which was at 20:00. This makes the possibility of rebound (and thus worse sleep) less likely. In children, stimulants are often given during the day to facilitate behavior during school hours, and not in the evening. This might increase the chance of rebound early in the evening, and lead to bedtime resistance and sleep problems. Kent et al. reported that children with ADHD derived substantial symptom reduction from Mph administered late in the afternoon, with no untoward effects on sleep.[37]

Regarding the effect of Mph on the *circadian* organization of the rest-activity rhythm, it delayed the onset of the least active period. This result was in accordance with the effects of medication on the sleep parameters, which were a delay in bedtime and sleep start, and longer sleep onset latency. A somewhat surprising result was an increased fragmentation of periods of rest and activity (IV). The value was still below that of NCs in the baseline comparison, so the increase might be seen as an effect towards normalization of fragmentation. The most likely explanation of the high baseline fragmentation level (IV) is that daytime activity levels may be continuously at a high level in ADHD, but interspersed with brief periods of a lower activity level in healthy controls, thus resulting in a higher variability in controls. This interpretation would then suggest that the Mph-induced increase in fragmentation could result from an increased number of brief periods of decreased activity, rather than by a continuously lowering of activity level. This is in line with the fact that the net decrease in daytime activity (M10) was slight and non-significant.

Age, sex, and seasonal effects were included in the analyses because of the previously established influence of these variables on sleep-wake parameters. Within the ADHD group, it was striking that females showed a higher mean activity count during the day than males. This is rather surprising, since in children with ADHD, it has been thought that girls more often show the inattentive subtype, with less profound motor hyperactivity, whereas boys are supposedly more often affected by the hyperactive/impulsive subtype of the disorder.[38] There is tentative evidence both for lack of differences at the symptom level between sexes in adult ADHD,[39] and for overrepresentation of the hyperactive/impulsive subtype among adult women with the disorder,[14] so the difference in activity level warrants further investigation. In our ADHD group, there were more women (65%) than men (38%) with a light, medium, or high physical component in their occupation, which may partly explain this difference (the correlation between physical component of occupation and M10 was 0.24). Differences in comorbid disorders between sexes may influence the activity level as well.

The most outstanding result with respect to age was that sleep seems to become more consolidated (as indicated by increased sleep efficiency, fewer wake bouts, and longer sleep bouts) in the ADHD group with age. These are remarkable findings given the literature on increasing sleep problems with age in the healthy population.[40] The findings may be related to a decline in hyperactive symptoms with age.[21]

Our study has some limitations that should be taken into account in future investigations of activity and sleep in adult ADHD. The presence of primary and secondary sleep disorders in adult ADHD is possible; a thorough investigation of such disturbances in adult ADHD has not yet been undertaken.

Our present work should be seen a first step in elucidating sleep-wake rhythms in adult ADHD and the effect of Mph. With respect to the latter, it should be mentioned that our compliance rate seemed rather low (20 out of 28 as measured with the Memos device). Although our definition of compliance may have led to labeling people as noncompliant when in fact they did take their medication (outside the 15-min limit), this result warrants careful monitoring of compliance in future medication trials. Counting of leftover pills suggested a higher compliance rate in our trial, but this is a less trustworthy measure of compliance, since participants can easily alter the number of leftover pills. The demonstration of increased sleep onset latency, decreased sleep efficiency, and shorter periods of uninterrupted sleep in adult ADHD subjects warrants more extensive and expensive research including polysomnography, circadian analyses of parameters like body temperature and melatonin, and a complete screening by a sleep clinician. Furthermore, even though we found no relation to symptoms of depression or anxiety, it would be important to examine the effect of other possible comorbid disorders. Other important issues for further research are: the long-term effects of stimulant treatment on sleep parameters, daytime sleepiness, effects of sleep disturbances on problems in cognitive functioning that have been related to ADHD, issues with respect to clinical responders versus non-responders, and ADHD subtypes.

In conclusion, we have established that adult ADHD is associated with elevated and less variable daytime activity, worse objective and subjective sleep quality, and a more rigid daily schedule of activity. Treatment with Mph improved sleep quality in spite of prolonging sleep onset latency and decreasing total sleep time. At present, one can only speculate on the potential mechanisms of the disturbed sleep in adult ADHD, and beneficial effects of Mph. In rather general terms, the presumed derailment of arousal regulation in adult ADHD appears not to be limited to the daytime. The reduction of consolidated periods of sleep within the night and the decreased sleep efficiency indicate a deficit in the ability to consolidate the sleep state. In agreement with the presumed normalizing action of Mph on daytime arousal regulation, it also appeared to normalize the nocturnal deficit, i.e., it promoted consolidated sleep by reducing the number of awakenings and increasing the average duration of within-night periods of uninterrupted sleep. Studies utilizing temperature or melatonin assessment under more controlled circumstances are needed to further evaluate the possibility of a circadian phase delay. Our data suggest that sleep problems are inherent in adult ADHD, both objectively and subjectively, and deserve further investigation including controlled circadian studies, polysomnography and a clinical sleep investigation. Our data also suggest that sleep problems are neither caused by nor worsened with stimulant treatment in this population. On the contrary, stimulants improve the quality of sleep in adults with ADHD.

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Abbreviations

ADHD	=	Attention Deficit Hyperactivity Disorder
Mph	=	methylphenidate
NC	=	normal control
IS	=	interdaily stability
IV	=	intradaily variability
RA	=	relative amplitude

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