The Effect of Stimulants on Nocturnal Motor Activity and Sleep Quality in Adults With ADHD: An Open-Label Case-Control Study

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Objective: Sleep disturbances are common in adults with attention-deficit/hyperactivity disorder (ADHD). In a case-control study, adult ADHD was associated with increased nocturnal motor activity and reduced self-perceived quality of sleep.

Method: Eight adults with DSM-IV–diagnosed ADHD (combined type, N = 7; inattentive type, N = 1) were treated with stimulants in open-label form at 8:00 a.m., 12:00 noon, and 4:00 p.m. The mean daily dose was 51 mg of methylphenidate (range, 30–90 mg) in 7 subjects and 30 mg of dextroamphetamine in 1 subject. Actimeters were used to assess nocturnal motor activity during 6 consecutive nights both at baseline and after 3 weeks of treatment. The data were compared with those of 8 matched normal controls.

Results: ADHD patients slept worse and showed significantly higher nocturnal motor activity at baseline compared with controls. No baseline differences between patients and controls were found in sleep latency, number of awakenings, and total time in bed. Changes from baseline to week 3 within the ADHD patients indicated improvement of sleep quality ($p = .05$) and reduction of Activity Level ($p = .10$) and Movement Index ($p = .07$) scores. When within-group changes were compared between ADHD subjects and controls, treatment with stimulants tended to be associated with a reduction of Activity Level ($p < .01$) and Movement Index ($p = .04$) scores and improved sleep quality ($p = .02$) in ADHD patients. Sleep latency, number of awakenings, and total time in bed were unaffected in within-group and between-group analyses.

Conclusion: The results should be interpreted cautiously given the open-label design and small sample size. Further study is warranted into the influence of stimulants on sleep in larger samples of ADHD patients by using controlled designs, multiple dose levels, and polysomnographic measures.

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Converging evidence now shows that attention-deficit/hyperactivity disorder (ADHD) in adults can be reliably diagnosed and that these adults have shown a pattern of psychiatric comorbidity, learning problems, and family-genetic correlates similar to that seen in ADHD in children.[1] Adult ADHD seems not to be a rare disorder; the prevalence of self-reported DSM-IV ADHD symptoms among a population of normal adults was consistent with an estimate of 4.7%.[2] Treatment with stimulants has been found to be effective in adult ADHD, as in childhood ADHD, and to result in clinically meaningful reductions of the core symptoms of ADHD.[3]

Sleep problems are common in patients with ADHD. According to parent reports, children with ADHD did differ from normal and psychiatric controls in having more sleep-related involuntary movements, such as restless sleep, sleep talking, and jerky movements.[4,5] The relationship between ADHD and sleep problems in pediatric samples has been further found to be complex and to depend on the presence of comorbid psychiatric disorders and treatment with stimulant medication. Dyssomnias, such as difficulty arising, bedtime resistance, and sleep-onset problems, were related to the presence of oppositional defiant disorder and the use of stimulant medication rather than to ADHD.[5] Moreover, though sleep-related involuntary movements were associated with ADHD combined type, sleep-related involuntary movements were even more strongly associated with the presence of comorbid separation anxiety disorder.[5] Similar results were obtained in 2 other questionnaire studies[6,7] on the association between sleep problems and ADHD. In a study[6] that included children and adolescents with ADHD and psychiatric and pediatric controls, 10.3% of the children with

ADHD who were treated with stimulants had severe sleep problems. The prevalence of serious sleep problems proved to be significantly higher than that among ADHD children not taking stimulants (5.8%) and among psychiatric and pediatric controls (6.7% and 0%, respectively).[6] Comorbid internalizing symptoms explained between 8% and 14% of the variance of sleep problems. Finally, most differences in sleep problems between adolescents with ADHD and age-matched normal controls disappeared when the analyses were adjusted for the presence of psychiatric comorbidity and treatment with stimulants. In the multivariate analysis, restless sleep and nocturnal awakening were associated with stimulant use and the presence of comorbid anxiety disorders rather than with ADHD per se.[7]

Sleep characteristics in children with ADHD have also been examined using objective methods such as actigraphy and polysomnography. Actimeters are small, wrist-worn computerized movement detectors that have been used in the objective and long-term assessment of human motor activity during both daytime and overnight.[8] Polysomnography involves the recording of multiple physiologic measures during sleep in a laboratory setting and allows one to examine the stages of electroencephalogram (EEG) sleep and architecture.[9,10] The results of polysomnographic studies in childhood ADHD have been inconsistent, however.[9,11] An about equal number of studies found sleep-onset latency to be longer,[12–14] shorter,[15–16] and the same[17–20] in ADHD as in control groups. Furthermore, the number of studies that did report differences in rapid eye movement (REM)[13,15,17,19,21] and non-REM[13,15,21–23] sleep between children with ADHD and controls and the number of studies that failed to document such differences[13,14,16,19,24] were in balance. The only consistent finding was that children with ADHD displayed more movements during sleep on actigraphy and that stimulant medication led to minor and nonpathologic changes in EEG sleep parameters.[11]

Few studies have examined the sleep problems of adults with ADHD. In a questionnaire study of 219 adults with ADHD,[25] 72% reported sleep-onset problems, 83% restless sleep, and 70% difficulty getting up in the morning. Sleep onset appeared to improve from, on average, 104 minutes to 26 minutes when the adults were treated with stimulants during daytime. Restless sleep diminished as well with the use of stimulants in a dosage administered at least 4 times per day. In our sample of 141 adults with ADHD,[26] 68% were found to have serious sleep problems at assessment and prior to the use of stimulant medication. This percentage was independent of the presence of comorbidity and the use of comedication.

In a case-control design,[27] we found that adult ADHD was associated with increased nocturnal motor activity, as measured by means of actigraphy, and reduced self-perceived quality of sleep. The present article reports on the effects of stimulants on nocturnal motor activity and sleep quality of adults with ADHD.

METHOD

Adult patients with ADHD were recruited from the Outpatient Clinic of the Mental Health Institute Delfland in Delft, the Netherlands. The diagnosis of ADHD according to the DSM-IV criteria was made on the basis of a semistructured interview in which the current and lifetime presence of DSM-IV criteria of ADHD as well as of comorbid Axis I and II disorders was systematically reviewed. The presence of ADHD symptoms in childhood was in all cases confirmed by family report. The patients were unmedicated for at least 8 weeks before entering the study. The study included normal control subjects who had never been treated for mental health problems, had no history of sleeping problems, and had used no medication other than oral contraceptives. Seven patients with ADHD were treated with methylphenidate in open-label form in a dose of 0.5 mg/kg/day in the first week and of 0.75 to 1.0 mg/kg/day in the second week, depending on efficacy and side effects.[3] One patient was treated with dextroamphetamine. The study was approved by the local Institutional Review Board Committee, and all participants gave their written informed consent.

Motor activity and subjective sleep characteristics were recorded twice, at baseline and 3 weeks later, for both patients and control subjects. Each time, the recording took place during 6 consecutive nights by means of a sleep log and an actimeter that was worn on the wrist of the nondominant arm.[8] The actimeter collects suprathreshold movements at 8-Hz sampling frequency, i.e., measures acceleration greater than 0.1*g* with filtering of the analog sensor signal by a band-pass filter of 0.25 to 3.00 Hz. All subjects were instructed to maintain their habitual 24-hour pattern of activities during the recording period. After recording, for each subject the mean Activity Level and the Movement Index were calculated as the dependent actimetric variables for the nocturnal period, defined as the period of lights out until getting up in the morning. The Activity Level is the mean number of counts over a 15-second interval. The Movement Index is the percentage of 15-second intervals with an activity count greater than zero that make up the period, irrespective of their distribution across that period. Dependent sleep log measures were total time in bed (h), sleep latency time (min), number of awakenings after sleep onset, and subjective sleep quality, assessed using a 5-point scale (ranging from 1 = excellent to 5 = very poor).

Statistical analysis was performed with SPSS for Windows (release 9.1, SPSS, Chicago, Ill.). Relationships between dependent sleep variables were explored by means of Spearman rank correlations. Nonparametric statistics (Mann-Whitney and Wilcoxon matched pairs ranking test) were used to test whether patients differed from controls at baseline, whether within-group changes between week 3 and baseline were significant, and whether

Table 1. Individual Data of Patients With Attention-Deficit/Hyperactivity Disorder (ADHD)

Patient	Age (y)	Subtype of ADHD	DSM-IV Comorbidity	Prior Sleep Problems	Dosage of Stimulants (mg/d)	Sleep Quality[a]		Activity Level[a]		Movement Index[a]	
						Wk 0	Wk 3	Wk 0	Wk 3	Wk 0	Wk 3
M	23	Combined	Dependent personality disorder	Yes	Methylphenidate (15)	3.0	2.3	4.1	2.9	9.5	7.0
F	33	Combined	Dysthymia, eating disorder NOS, borderline personality disorder	Yes	Methylphenidate (40)	3.4	2.5	2.5	1.8	6.0	5.6
M	21	Inattentive	No	Yes	Dextroamphetamine (30)	2.5	2.2	2.8	1.7	10.4	9.1
M	28	Combined	No	Yes	Methylphenidate (70)	1.5	1.3	2.0	1.4	7.0	5.4
F	44	Combined	No	No	Methylphenidate (45)	2.3	2.1	1.3	2.1	4.4	6.3
M	21	Combined	No	Yes	Methylphenidate (45)	2.0	2.0	2.2	1.7	6.9	4.5
M	28	Combined	No	Yes	Methylphenidate (90)	1.8	2.0	1.7	2.2	7.3	6.5
F	37	Combined	Major depressive disorder	No	Methylphenidate (55)	2.7	2.5	1.9	0.6	8.4	2.9

[a]Lower scores indicate improvement.

changes within patients with ADHD were significantly different from changes within controls. Testing was 2-tailed. Given the small sample size and the exploratory setup of the study, the level of statistical significance was set at .10.

RESULTS

Eight patients with ADHD (5 males, 3 females, all white) completed a second actimetric assessment after treatment with methylphenidate (N = 7) and dextroamphetamine (N = 1). These 8 patients were compared with 8 control subjects (4 males, 4 females, all white) who were of similar age, educational level, and socioeconomic status and for whom a second actimetric assessment was available. There were no significant differences in mean ± SD age between patients (29.4 ± 8.2 years) and controls (33.1 ± 7.2 years). All patients received a primary diagnosis of ADHD (combined type, N = 7; inattentive, N = 1). Three patients had comorbid disorders (Table 1). None had an actual substance use disorder and none used comedication. Six patients had prior sleep problems. The mean dosage of methylphenidate was 51 mg/day, and the range was 15 to 90 mg/day. One subject was treated with dextroamphetamine in a dose of 30 mg/day. Both stimulants were given at 8:00 a.m., 12:00 noon, and 4.00 p.m. Clinical efficacy was assessed on the basis of changes in the Clinical Global Impressions-Severity of Illness scale (CGI-S)[28] and was found to be efficacious in all patients.

The individual data of the ADHD patients are summarized in Table 1 and the group results in Table 2. At baseline, sleep latency correlated with sleep quality, total time in bed, and number of awakenings after sleep onset (Spearman r = 0.52, p < .05; r = 0.43, p < .10; and r = 0.50, p < .05, respectively). Activity Level and Movement Index were further strongly correlated (r = 0.90, p < .001). The only correlation between subjective and actigraphic sleep measures was between sleep latency and Activity Level (r = .44, p < .10).

Table 2. Descriptives of Dependent Variables (mean ± SD) and Results of Group Analyses for Patients With Attention-Deficit/Hyperactivity Disorders (ADHD) vs. Controls

Variable	ADHD (N = 8)		Controls (N = 8)	
	Wk 0	Wk 3	Wk 0	Wk 3
Total time in bed (h)	7.7 ± 0.8	7.1 ± 0.8	7.4 ± 0.4	7.1 ± 1.0
Sleep latency (min)	26 ± 21	21 ± 18	11 ± 9	13 ± 7
Number of awakenings	1.0 ± 0.9	1.1 ± 0.9	0.9 ± 0.7	0.7 ± 1.1
Sleep quality (range, 1–5)	2.4 ± 0.6*	2.1 ± 0.4‡*	1.9 ± 0.2	1.9 ± 0.4
Activity level	2.3 ± 0.9***	1.8 ± 0.7**	1.0 ± 0.3	1.8 ± 0.6‡
Movement index	7.5 ± 1.9***	5.9 ± 1.8†**	4.0 ± 1.3	4.7 ± 1.1

*p < .10; **p < .05; ***p < .01. Asterisks refer to differences between ADHD and controls at baseline and to between-group changes between baseline (Wk 0) and endpoint (Wk 3).
†p < .10; ‡p < .05. Daggers refer to within-group differences between baseline and endpoint.

At baseline, no differences between patients and controls were found for the total time in bed, sleep latency, and number of awakenings. ADHD patients, however, tended to have slept significantly less well than the controls (Z = –2.94, p = .08). This difference was due to the ADHD subjects with comorbid disorders rather than to the subjects with ADHD only. In addition, the patients showed significantly higher nocturnal motor activity, as reflected in higher Activity Level and Movement Index scores (Z = –2.94, p = .002 and Z = –3.05, p = .001, respectively). These effects were independent of comorbidity.

Among the patients with ADHD, sleep quality was improved at week 3 compared with baseline (Z = –1.95, p = .05). Further, Activity Level and Movement Index were reduced in ADHD patients at week 3 compared

with baseline (Z = –1.65, p = .10 and Z = –1.82, p = .07). These changes among the patients with ADHD between week 3 and baseline appeared to be independent of comorbidity and stimulant dose. In the controls, in contrast, Activity Level increased from baseline to week 3 (Z = –2.24, p = .03). When the changes from baseline to week 3 were compared between the patients with ADHD and controls, total time in bed, sleep latency time, and number of awakenings proved to be unaffected by stimulant treatment. Treatment with stimulants in patients with ADHD, after controlling for changes in controls, did appear, however, to be associated with an improved subjective sleep quality (Z = –2.27, p = .02) and reduction of nocturnal motor activity. The latter effect was reflected by greater changes in ADHD than in controls for Activity Level (Z = –2.73, p < .01) and Movement Index (Z = –2.10, p = .04).

DISCUSSION

The present findings of increased nocturnal motor activity in adults with ADHD are in concordance with earlier data in children.[11] Our findings are not confounded by the use of medication since baseline assessment occurred prior to the start of the treatment with stimulants. The differences between patients and controls at baseline appeared to be independent of the presence of comorbid psychiatric disorders.

All patients with ADHD revealed a clinical response to stimulant treatment. It is well known that insomnia in patients taking stimulants may be due to the awakening effect of these medications or may be ascribed to rebound effects of stimulants after wearing off. On the other hand, sleep initiation problems in ADHD may result from the presence of interfering symptoms like restlessness and overactivity. Clinical experience in childhood and adult ADHD suggests that in those cases, stimulants given during the daytime or even in the evening may improve sleep.[29] A formal study confirmed the beneficial effects of methylphenidate on sleep EEG and behavior of children with ADHD.[30] The present preliminary data show that stimulants given during the daytime in adult patients with ADHD both reduced nocturnal motor activity that was objectively assessed by means of an actimeter and improved self-reported quality of sleep. The effect size of the change in Movement Index was 0.9, which is larger than that in subjectively reported sleep quality (0.6), and lends further credibility to the results. From a clinical perspective, all 6 patients with ADHD who had reported prior sleep problems were found to have significant improvement in sleep parameters. It should be noted that the between-group differences in Activity Level in week 3 may be inflated because of changes in the control group rather than in patients with ADHD.

The stimulant effects on sleep appeared to be unaffected by comorbidity or stimulant dose. Since, however, no attempt was made to evaluate different dosages in the same patient, the issue of dose-response relationship was not fully explored, nor was the influence of the time of the day when stimulants were taken.

It is of interest to consider the potential relationship between sleep quality and daytime behavior. Clinical experience indicates that sleep problems may interfere with optimal performance during the daytime, and even may induce or aggravate symptoms of inattention and hyperactivity. Such interference has particularly been reported for subjects with sleep-apnea syndrome.[31,32] The reverse may be true as well, however, in that severity of ADHD determines the risk for sleep problems. Further, some patients with ADHD do seem to need less sleep than people without ADHD, without adverse consequences for daytime behavior.

Given that the plasma half-life of methylphenidate is between 2 and 3 hours and the last dose in the present study was administered at 4:00 p.m., the beneficial influence on nocturnal sleep seems to be a spin-off effect of a reduction of ADHD symptoms and a better overall adjustment over the day rather than a direct medication effect on ADHD symptoms at night. Support for this possibility may be found in recent findings that children with ADHD were more sleepy during the day when compared with controls, as shown by a greater number of sleep periods and a shorter sleep latency in a Multiple Sleep Latency Test.[9] This sleepiness during the day correlated significantly with severity of ADHD symptoms and suggests that an arousal dysfunction underlies ADHD. Stimulant treatment may improve this arousal dysfunction and produce a consolidated wakefulness during the day and better sleep at night. An alternative possibility is that stimulants exert a longer-lasting direct effect on chronobiological brain functioning by a yet unknown mechanism that results in improved sleep.

The results of this open-label study are limited by its small sample size and lack of controlled design. Further study into the influence of stimulants on sleep in larger samples of ADHD patients, using controlled designs, multiple dose levels, and variation in timing of dosage and including polysomnographic measures, is warranted.

Drug names: dextroamphetamine (Dexedrine and others), methylphenidate (Ritalin and others).

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