Effect of Melatonin on Sleep, Behavior, and Cognition in ADHD and Chronic Sleep-Onset Insomnia

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ABSTRACT

Objective: To investigate the effect of melatonin treatment on sleep, behavior, cognition, and quality of life in children with attention-deficit/hyperactivity disorder (ADHD) and chronic sleep onset insomnia. **Method:** A total of 105 medication-free children, ages 6 to 12 years, with rigorously diagnosed ADHD and chronic sleep onset insomnia participated in a randomized, double-blind, placebo-controlled trial using 3 or 6 mg melatonin (depending on body weight), or placebo for 4 weeks. Primary outcome parameters were actigraphy-derived sleep onset, total time asleep, and salivary dim light melatonin onset. **Results:** Sleep onset advanced by 26.9 ± 47.8 minutes with melatonin and delayed by 10.5 ± 37.4 minutes with placebo ($p < .0001$). There was an advance in dim light melatonin onset of 44.4 ± 67.9 minutes in melatonin and a delay of 12.8 ± 60.0 minutes in placebo ($p < .0001$). Total time asleep increased with melatonin (19.8 ± 61.9 minutes) as compared to placebo (−13.6 ± 50.6 minutes; $p = .01$). There was no significant effect on behavior, cognition, and quality of life, and significant adverse events did not occur. **Conclusion:** Melatonin advanced circadian rhythms of sleep-wake and endogenous melatonin and enhanced total time asleep in children with ADHD and chronic sleep onset insomnia; however, no effect was found on problem behavior, cognitive performance, or quality of life. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(2):233–241. **Key Words:** melatonin, insomnia, attention-deficit/hyperactivity disorder.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity/impulsivity, or both, and is one of the most common psychiatric disorders of childhood (American Psychiatric Association, 1994). Approximately one third of medication-free children with ADHD experiences chronic sleep-onset insomnia (SOI) (Corkum et al., 1999; Stein, 1999). This persistent disability to fall asleep at the desired time in the evening may exacerbate daytime mood, behavioral, and/or cognitive problems (Sadeh et al., 2003).

The safety and efficacy of melatonin treatment for SOI in children without ADHD have been documented in several studies (Smits et al., 2001; 2003; Van der Heijden et al., 2005a). Melatonin efficacy has not been

studied in medication-free children with ADHD and SOI; however, this patient group is of special interest. First, medication-free children with ADHD and SOI have a delayed evening increase in endogenous melatonin levels (Van der Heijden et al., 2005b) and this phase delay predicted a stronger sleep phase–normalizing effect of exogenous melatonin in children without ADHD (Van der Heijden et al., 2005a). Second, because treatment of sleep-related disorders other than insomnia improved daytime function in children with ADHD (Ali et al., 1996; Walters et al., 2000), the treatment of insomnia may be expected to do so as well and thus may have important consequences for ADHD treatment strategies in health care settings.

We investigated whether melatonin treatment could improve objective and subjective measures of sleep, behavior, cognitive performance, and quality of life in medication-free children diagnosed with ADHD and SOI.

METHOD

Subjects

A total of 176 children with possible ADHD were referred for participation in this trial to outpatient clinics for sleep-wake disorders of the Gelderse Vallei General Hospital and Kempenhaeghe by seven Dutch community mental health institutions and three pediatric hospital departments. Twenty-eight children were recruited through advertisements in magazines, newspapers, or via the Dutch ADHD patient support center. Of these 204 children, 107 enrolled in the present study after diagnostic evaluation (Fig. 1). Inclusion criteria were 6 to 12 years old, diagnosis of ADHD and SOI, and written informed consent obtained from parents. Exclusion criteria were total IQ <80, pervasive developmental disorder, chronic pain, known disturbed hepatic or renal function, epilepsy, earlier use of melatonin, and use of stimulants, neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics, or β-blockers within 4 weeks before enrollment.

Clinical Assessment

All 204 children were assessed by a psychologist (K.B.H.) and a board-certified child and adolescent psychiatrist (W.B.G.). ADHD was diagnosed in accordance with guidelines of the American Academy of Pediatrics (2000) and American Academy of Child and Adolescent Psychiatry (1997) and included clinical history, Diagnostic Interview Schedule for Children-Parent form (Shaffer et al., 1996), Child Behavior Checklist (CBCL; Achenbach, 1991a), and Teacher's Report Form (TRF; Achenbach, 1991b). Subtypes of ADHD were determined according to *DSM-IV*. A shortened IQ test (WISC-R Dutch version: Block Design, Vocabulary [De Bruin et al., 1986]) was administered when IQ had not been assessed previously and school performance had been subaverage in the past 3 years.

SOI was defined as (1) complaints of sleep-onset problems expressed by parents and/or child, (2) occurrence on at least 4 days/week for longer than 1 year, (3) average sleep onset later than 8:30 PM for children at age 6 years and for older children 15 minutes later per year, and (4) average sleep latency exceeding 30 minutes (Van der Heijden et al., 2005a). The diagnostic procedures included clinical history, 1-week 24-hour actigraphy measurement, Dutch Sleep Disorders Questionnaire (Sweere et al., 1998), and Children's Sleep Hygiene Scale (Harsh et al., 2002).

Study Design and Conduct

A 4-week randomized, double-blind, placebo-controlled study, immediately following a 1-week baseline period, was conducted between November 2001 and June 2005. The protocol was approved by the institutional review board at each center, as a multicenter trial by the Central Committee on Research Involving Human Subjects, and registered in the International Standard Randomized Controlled Trial Number Register (ISRCTN-47283236). The trial was performed according to the 1997 European Guidelines for Good Clinical Research Practice in children and followed the 1983 revised provisions of the 1975 Declaration of Helsinki.

Participants were randomly assigned (1:1 ratio) to receive melatonin (3 mg when body weight <40 kg [$n = 44$]; 6 mg when body weight >40 kg [$n = 9$]) in fast-release tablets (Pharma Nord, Denmark) or identical-appearing placebo tablets at 7:00 PM. These pharmacological doses had previously been proved effective and safe in children (Smits et al., 2001, 2003). Treatment adherence was assessed after 3 weeks of treatment by medication counts. All of the measurements took place at baseline and during the fourth treatment week. Parents were called weekly to monitor progress and discuss possible problems. Children were allowed to go to bed whenever they felt tired rather than being tied to a scheduled bedtime. Participants were not allowed to start or change therapeutic interventions during the study. No assessments took place during or within 3 days following holidays or clock time transitions. All of the participants were offered melatonin treatment after the end of the study.

Outcome Measures

Sleep. Sleep was estimated using actigraphy (Actiwatch, Cambridge Neurotechnology Ltd., Cambridge, UK) and sleep logs on seven consecutive days, at baseline, and during the fourth treatment week. Actigraphs, worn on the nondominant wrist, recorded the amount of movement at 1-minute epochs, 24 hours/day. Actigraphy data were converted into sleep parameters by the validated automatic Actiwatch scoring algorithm (Kushida et al., 2001), using sleep log–derived lights out and rise time, and by subsequent manual verification based on sleep log data: sleep onset, sleep latency (time from lights out until sleep onset), wake up time; total time asleep, sleep efficiency, moving time (percentage time spent moving during assumed sleep period). Furthermore, nonparametric variables were derived from actigraphy data as described previously (Van Someren et al., 1999): interdaily stability (degree of resemblance between the activity patterns on individual days), intradaily variability (fragmentation of periods of sleep and activity), L5 (average activity during the least-active 5 hours). (Detailed information on outcome parameters is available via the ArticlePlus feature at the *Journal's* Web site

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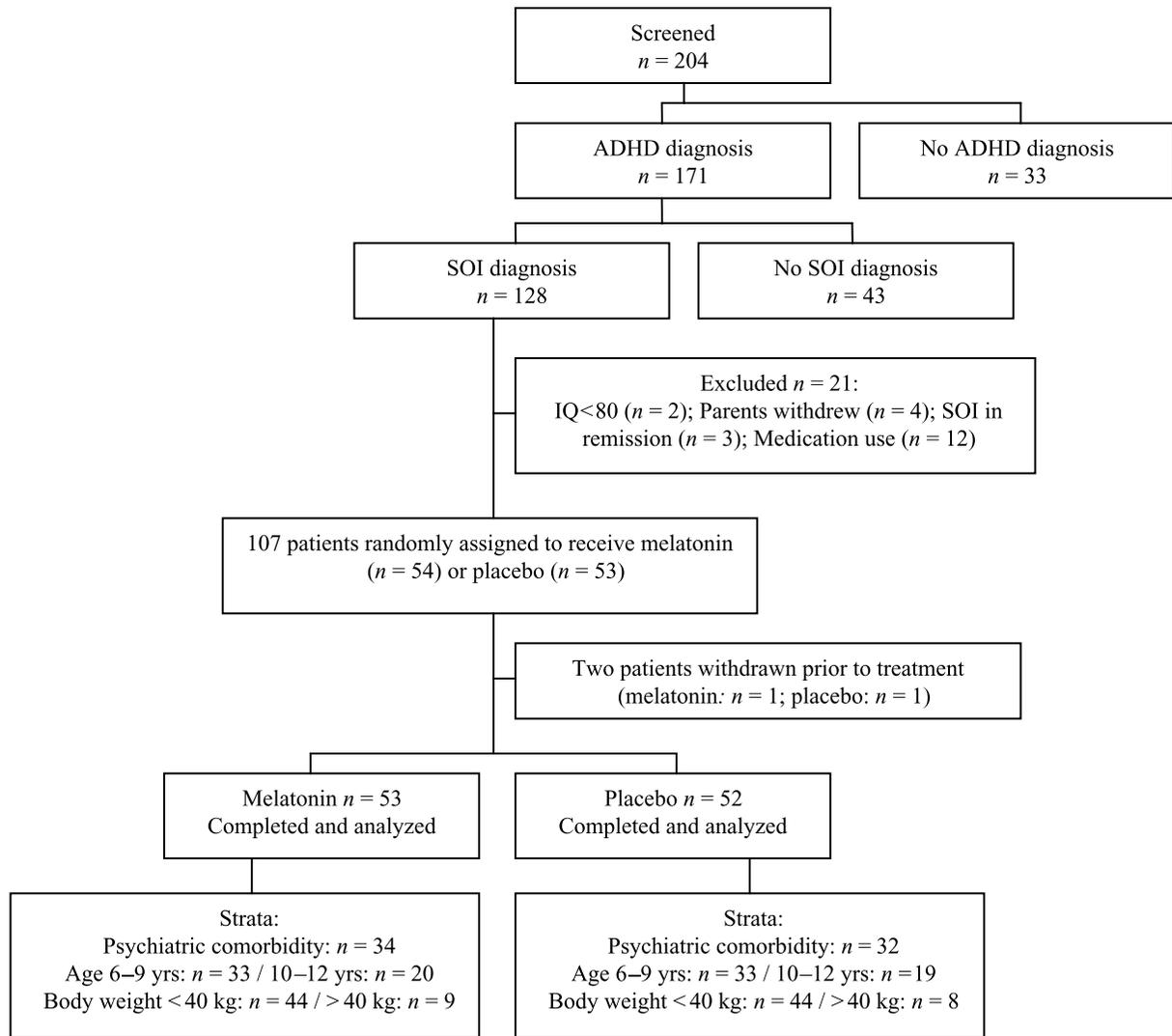
Fig. 1 Participant flow diagram. SOI = sleep-onset insomnia.

www.jaacap.com). Primary sleep outcome parameters were sleep onset, total time asleep, and sleep log item difficulty falling asleep (averaged over 7 days, on a scale of 1 [not difficult] to 5 [very difficult]).

Dim Light Melatonin Onset (DMLO). DLMO is the clock time at which the endogenous melatonin level starts to rise in the subjective evening and is considered the most reliable phase marker of the biological clock rhythm (Klerman et al., 2002). DLMO was assessed at baseline and on the first evening of the fourth treatment week. Hourly samples of saliva from 6:00 to 10:00 PM (6–7 years old), or 7:00 to 11:00 PM (8 to 12 years old) were obtained by chewing on a cotton plug for 1 minute (Salivetten, Sarstedt Nümbrecht, Germany). No medication was taken on the evening of the salivary sample collection because medication intake may alter the endogenous levels of melatonin. To prevent suppression of melatonin secretion by bright light, curtains needed to be closed, and only one dim light was allowed during the entire measurement period. DLMO was defined as the linearly interpolated time at which the melatonin concentration first reached 4 pg/mL.

Melatonin concentrations were measured as described previously (Nagtegaal et al., 1998).

Problem Behavior, Cognitive Performance, and Quality of Life

The primary prespecified outcome parameter was the averaged grade (1 = very severe; 10 = none) on three individually defined (spontaneously, not from a checklist), most serious, and common core problems of the child, given by parents as well as teachers.

Emotional and behavioral problems were assessed with the CBCL and TRF, which consisted of 120 items (response scale: 0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true), and yielding a total score and eight syndrome scale scores (high scores indicating more problems).

Interference control is the ability to ignore information linked to an inappropriate response tendency and was shown to be impaired in ADHD (Cornoldi et al., 2001). The Eriksen task is a

computerized choice reaction time (RT) task of interference control. Subjects had to respond on the direction of a target arrow, while, occasionally, a conflict occurred between this designated response and a competing response tendency elicited by incongruent flanking arrows, which they had to ignore (6 blocks of 60 stimuli, of which 1 was a practice block). Compared with the congruent and neutral flankers, the conflicting information produced by the incongruent flankers has been reported to lead to increased error incidence (EI_Δ, percentage) and delayed RTs (RT_Δ, milliseconds [Ridderinkhof et al., 2005]).

Sustained attention was shown impaired in ADHD with improvements after stimulant treatment (Riccio et al., 2001). We administered the Sustained Attention Dots Task (Amsterdam Neuropsychological Tasks [De Sonneville, 1999]), a computerized visual task in which subjects were presented a continuous and consecutive series of 300 target (33%) and nontarget (67%) asymmetric dot configurations in a pseudo-random fashion. Subjects pushed a "yes" button whenever a target appeared and a "no" button after a nontarget signal, after which the next stimulus was presented immediately (i.e., self-paced). The task parameters were inaccuracy (%) and task completion time (seconds).

The TNO-AZL Questionnaire for Children's Health-Related Quality of Life, Parent Form (TACQOL-P; Vogels et al., 2000) consisted of 63 items on whether specific problems occurred or feeling had been present in recent weeks, with a 3-point Likert response scale, yielding a total sum score (maximum, 224: highest quality of life) as well as scores on seven subdomains.

Adverse Events

Parents reported adverse events in an unstructured interview (K.B.H.) 3 weeks after the start of study treatment. A 2-year follow-up was conducted using a self-constructed, structured questionnaire with items on various treatment aspects and adverse effects.

Data Analysis

A total of 107 patients was selected for enrollment. (sample size calculation is available via the ArticlePlus feature at the *Journal's* Web site *www.jaacap.com*). Randomization was performed by a hospital pharmacist not connected to the study in blocks of four to keep the number of patients in each treatment group closely balanced at all times. The following stratification criteria were used: (1) presence of psychiatric comorbidity (disruptive behavior disorder [$n = 59$]; anxiety disorder [$n = 16$]; depressive disorder [$n = 1$]), (2) age category (6–9 years [$n = 66$]; 10–12 years [$n = 39$]), and (3) body weight (<40 kg [$n = 88$]; = 40 kg [$n = 17$]). Investigators and participants were unaware of treatment allocation. The code was broken after all of the children completed treatment and data were recorded (October 2005).

Comparisons of demographic and clinical characteristics between treatment groups were conducted using independent samples *t* test for continuous variables with a normal distribution, Mann-Whitney *U* test when distribution was not normal, and Pearson χ^2 test for discrete categorical variables. Between-group differences in mean day length (hours) and mean rate of change in day length (hours per week) were analyzed to control for possible confounding.

Analyses of between-group differences in pre- to posttreatment changes were conducted using general linear model (GLM) repeated-measures analysis of variance for continuous variable, and with Pearson χ^2 tests for categorical variables. The relationship of pre- to posttreatment changes with variables of interest was analyzed with linear regression analysis. Between-group differences in adverse events were analyzed with the Fisher exact test.

Analyses were conducted using SPSS, 12.0.1 (SPSS, Inc., Chicago, IL) on an intention-to-treat basis (significance $p = .05$, two-sided). To compensate for the increased probability of a type I error, Bonferroni correction of *p* values was applied when multiple tests were conducted on questionnaire subscales (CBCL, TRF, TACQOL), calculated by multiplying the resulting *p* values by the number of outcomes being tested (corrections are indicated).

RESULTS

Baseline Demographic and Clinical Characteristics

Of 107 patients, 105 received melatonin ($n = 53$) or placebo ($n = 52$). Two were withdrawn because shortly after assignment they started another treatment without permission (Fig. 1). At baseline, there were no significant between-group differences in demographic variables, clinical characteristics, mean day length, or mean rate of change in day length (Table 1).

TABLE 1
Demographic and Clinical Characteristics

	Melatonin ($n = 53$)	Placebo ($n = 52$)	*p* Value
Age, mean ± SD (y)	9.1 ± 2.3	9.3 ± 1.8	.64[a]
Body weight (kg)	31.8 ± 10.3	32.7 ± 9.7	.67[a]
Male, no. (%)	35 (66.0)	43 (82.7)	.051[b]
ADHD subtype, no. (%)			
ADHD-C	41 (77.4)	36 (69.2)	.34[b]
ADHD-I	9 (17.0)	13 (25.0)	.31[b]
ADHD-HI	2 (3.8)	2 (3.8)	.98[b]
Psychiatric comorbidity (%)			
Disruptive behavioral disorder	31 (58.5)	28 (53.8)	.71[b]
Anxiety disorder	7 (13.2)	9 (17.3)	.53[b]
Depressive disorder	1 (1.9)	0 (0)	.32[b]
Insomnia score (SDQ)	2.6 ± 0.5	2.6 ± 0.6	.69[c]
PLMS/RLS score (SDQ)	1.6 ± 0.7	1.6 ± 0.6	.84[c]
OSAS score (SDQ)	1.2 ± 0.3	1.2 ± 0.3	.81[c]
Sleep hygiene score (CSHS)	55.4 ± 10.2	57.2 ± 10.2	.40[c]

Note: ADHD = attention-deficit/hyperactivity disorder; ADHD-C = attention-deficit/hyperactivity disorder combined subtype; ADHD-I = attention-deficit/hyperactivity disorder inattentive subtype; ADHD-HI = attention-deficit/hyperactivity disorder hyperactive/impulsive subtype; SDQ = Dutch Sleep Disorders Questionnaire (scale 1 = never to 5 = always); PLMS/RLS = periodic limb movement disorder/restless legs syndrome; OSAS = obstructive sleep apnea; CSHS = Children's Sleep Hygiene Scale (scale 25–150, higher values indicate worse sleep hygiene).

[a] Independent samples *t* test.
[b] Pearson χ^2 test.
[c] Mann-Whitney *U* test.

Efficacy Measures

Pre- as well as posttreatment data were available from a mean (± SD) of 69.6% ± 17.4% (range, 32.4%–86.7%) of the participants, varying with outcome measure. (Raw data are available via the ArticlePlus feature at the *Journal's* Web site *www.jaacap.com*). Missing data mainly resulted from technical problems (actigraphy), insufficient volume of collected saliva (DLMO), technical problems or refusal of children to perform the task (cognitive performance), partial completion of questionnaires, loss by participants, and nonadherence to instructions.

Sleep

Mean actigraphic estimate of sleep onset advanced by 26.9 ± 47.8 minutes with melatonin, whereas there was a delay of 10.5 ± 37.4 minutes with placebo ($p < .0001$; Table 2). After melatonin, 20 (48.8%) of 41 children for whom actigraphy data were available showed an advance of sleep onset >30 minutes, whereas this was 5 of 39 (12.8%) after placebo ($\chi^2 = 12.0$; $p = .001$). There was an increase in mean total time asleep of 19.8 ± 61.9 minutes with melatonin and a decrease of 13.6 ± 50.6 minutes with placebo ($p = .01$). As compared with placebo, the melatonin group showed a significant decrease in sleep latency ($p = .001$), increase in sleep efficiency ($p = .01$), and decrease of nocturnal restlessness (L5; $p = .03$). Between-group differences in changes of other actigraphic sleep measures were not significant. The mean score on sleep log item difficulty falling asleep decreased by 1.2 ± 1.3 points (35.3% of baseline) with melatonin and by 0.1 ± 0.8 points (4.3% of baseline) with placebo ($p < .0001$).

TABLE 2
Outcome Variables

Variable	Melatonin			Placebo			p Value[a]
	Baseline	Treatment	Change	Baseline	Treatment	Change	
DLMO (hr:min)	20:37 ± 0:56	19:53 ± 1:06	−0:44 ± 1:07	20:32 ± 0:54	20:45 ± 1:06	+0:13 ± 0:59	<.0001*
Sleep							
Sleep onset (hr:min)	21:40 ± 0:59	21:13 ± 0:58	−0:27 ± 0:48	21:38 ± 0:47	21:48 ± 0:48	+0:10 ± 0:37	<.0001*
Sleep latency (min)	53.0 ± 22.0	31.7 ± 30.7	−21.3 ± 33.0	47.3 ± 23.2	50.4 ± 30.4	+3.0 ± 31.7	.001*
Total time asleep (min)	518.9 ± 48.3	538.7 ± 55.0	+19.8 ± 61.9	533.8 ± 47.8	520.2 ± 47.5	−13.6 ± 50.6	.01*
Sleep efficiency (%)	80.1 ± 5.5	82.7 ± 7.5	+2.6 ± 8.9	82.4 ± 5.7	80.3 ± 5.9	−2.1 ± 7.1	.011*
Difficulty falling asleep[b]	3.4 ± 0.9	2.2 ± 0.9	−1.2 ± 1.3	3.2 ± 0.7	3.1 ± 1.0	−0.1 ± 0.8	<.0001*
Problem behavior							
Core problems_parents	4.0 ± 1.3	4.8 ± 1.3	+0.7 ± 0.9	4.3 ± 1.3	4.5 ± 1.2	+0.2 ± 0.8	.002*
Core problems_teacher	4.6 ± 1.0	5.3 ± 1.1	+0.7 ± 0.9	4.4 ± 1.2	4.9 ± 1.4	+0.5 ± 1.0	.41
CBCL	63.0 ± 16.0	55.1 ± 18.4	−8.0 ± 8.8	61.5 ± 21.8	45.3 ± 25.7	−16.2 ± 18.2	.083
TRF	46.1 ± 20.7	42.1 ± 19.1	−4.0 ± 12.5	52.2 ± 26.1	48.1 ± 25.0	−4.0 ± 16.4	.29
Quality of life							
TACQOL-P_total	170.4 ± 19.9	179.1 ± 21.8	+8.7 ± 13.0	168.8 ± 22.5	176.9 ± 22.5	+8.1 ± 9.1	.82
Cognition							
Interference control (EFT)							
ΔReaction time[c] (ms)	50.1 ± 37.1	33.1 ± 33.0	−17.0 ± 43.2	41.8 ± 27.8	32.3 ± 25.4	−9.5 ± 34.4	.37
ΔError incidence[d] (%)	3.4 ± 4.0	3.8 ± 3.5	+0.4 ± 4.5	3.8 ± 3.7	3.2 ± 3.5	−0.6 ± 3.6	.28
Sustained attention (SADT)							
Inaccuracy (%)[e]	12.6 ± 7.6	12.2 ± 7.2	−0.3 ± 4.5	12.0 ± 6.7	12.34 ± 7.3	+0.4 ± 5.6	.52
Task completion time (s)	469.0 ± 153.0	410.5 ± 142.6	−58.5 ± 77.8	489.4 ± 187.1	428.2 ± 171.9	−61.2 ± 85.5	.58

Note: DLMO = salivary dim light melatonin onset; CBCL = Child Behavior Checklist, total score; TRF = Teacher's Report Form, total score; TACQOL-P = TNO-AZL Questionnaire for Children's Health-Related Quality of Life, Parent Form; EFT = Eriksen Flanker Task; SADT = Sustained Attention Dots Task (Amsterdam Neuropsychological Tasks).

[a] General linear model repeated-measures test on group differences in pre- to posttreatment changes.

[b] Mean difficulty falling asleep as reported by parents, averaged over 7 days on a scale of 1 (not difficult) to 5 (very difficult).

[c] Difference in reaction time between incongruent and congruent trials.

[d] Difference in error incidence between incongruent and congruent trials.

[e] Percentage of misses plus false alarms relative to the total number of trials.

* Statistically significant difference ($p = .05$, two-sided).

DMLO

Melatonin-treated children showed an advance in DLMO of 44.4 ± 67.9 minutes compared with a delay of 12.8 ± 60.0 minutes in children receiving placebo (p < .0001). In melatonin, pre- to posttreatment changes in sleep onset showed a significant linear relationship with pretreatment values of DLMO (R = 0.42; p = .008), indicating that more delayed DLMO values at baseline associated with stronger advances of sleep onset after melatonin treatment. This relationship was not significant in placebo (R = 0.078; p = 0.645). In melatonin, pre- to posttreatment changes in DLMO were not significantly related with pre- to posttreatment changes in sleep onset (R = 0.30; p = .124). Between-group differences in changes of DLMO were not significantly related to presence of comorbid psychiatric disorders.

Problem Behavior, Cognitive Performance, and Quality Of Life

Core Problems. The mean score at baseline was 4.0 ± 1.3 in melatonin and 4.3 ± 1.3 in placebo (maximum, 10: no problems). The most frequently reported problems were easy to anger (36.0%), sleep-onset problems (31.8%), and attention problems (23.3%). Mean score improved by 0.7 ± 0.9 (18.4% of baseline) with melatonin by and 0.2 ± 0.8 (3.7% of baseline) with placebo (p = .002). This group difference lost statistical significance after removing core symptoms related to sleep. Between-group differences in changes of teacher-reported core problems were not significant.

Behavioral and Emotional Symptoms. Between-group differences in pre- to posttreatment changes of mean total CBCL (p = .083) and TRF (p = .294) scores were not significant. Improvements on the aggressive behavior subscale of CBCL were significantly smaller with melatonin (−0.6 ± 3.4) compared with placebo (−6.2 ± 6.9; Bonferroni corrected p = .024). Changes in total CBCL and TRF scores were not related to changes in actigraphy-derived sleep onset, total time asleep, or sleep log–derived difficulty falling asleep.

Interference Control. At baseline, mean RT on incongruent trials was significantly slower (696.8 ± 146.4 seconds) than on congruent trials (650.8 ± 140.1 seconds; p < .0001), and EI on incongruent trials (7.8% ± 6.4%) was significantly higher than on congruent trials (4.2% ± 4.2%; p < .0001). These data indicate a significant effect of congruence on interference control. Melatonin

significantly reduced RT_Δ of correct responses with 17.0 ± 43.2 milliseconds, indicating an improvement of interference control; however, the difference with placebo (9.5 ± 34.4 milliseconds) was not significant (p = .37). Between group-differences in changes of EI_Δ were also not significant (p = .28).

Sustained Attention. Neither mean task completion time nor inaccuracy changed significantly with melatonin as compared to placebo (p = .58 and p = .52, respectively).

Quality of Life. Mean total TACQOL-P score at baseline was 170.4 ± 19.9 in melatonin and 168.8 ± 22.5 in placebo (maximum, 224). Neither between-group differences in changes of total TACQOL-P score nor Bonferroni-corrected changes on any of the seven subscales were significant. There was no significant relationship of changes in total TACQOL-P score with changes in actigraphy-derived sleep onset, total time asleep, or sleep log–derived difficulty falling asleep.

Adverse Events

The number of adverse events did not differ significantly between melatonin and placebo (Table 3) nor between the 3-mg (8/44) and 6-mg (2/9) treated groups (p = 1.00). Five patients had one adverse event, four patients had two, and one had three adverse events. There were no discontinuations or withdrawals caused by adverse events, and none of the adverse events required treatment.

TABLE 3
Adverse Events

Adverse event	Melatonin (n = 53), No. (%)[a]	Placebo (n = 52), No. (%)[a]	p Value[b]
Headache	3 (5.7)	0 (0)	.24
Hyperactivity	3 (5.7)	0 (0)	.24
Dizziness	2 (3.8)	0 (0)	.50
Abdominal pain	2 (3.8)	0 (0)	.50
Nose bleeding	1 (1.9)	0 (0)	1.00
Itching lumps on the skin	1 (1.9)	0 (0)	1.00
Painful lumps on the skin	1 (1.9)	0 (0)	1.00
Diarrhea	1 (1.9)	0 (0)	1.00
Decrease of mood	1 (1.9)	0 (0)	1.00
Maintenance insomnia	1 (1.9)	0 (0)	1.00

[a] Patients could report more than one event.
[b] Fisher exact test.

Follow-up at 2 years after participation yielded 24 of 26 completed questionnaires (2 families were untraceable): 19 of 24 still used melatonin (4.4 ± 2.0 mg at 7:42 PM $\pm$ 50 minutes), 1 used it occasionally, and 4 stopped after 17.23 ± 3.3 months (reasons: remission [$n = 3$], dizziness and drowsiness [$n = 1$]). Seven of 24 parents reported one or more of the following adverse events: bedwetting ($n = 2$), abnormal feces ($n = 2$), drowsiness ($n = 2$), dizziness ($n = 1$), sleep maintenance problems ($n = 1$), skin pigment changes ($n = 1$), and decreased mood ($n = 1$).

DISCUSSION

This is the first randomized, placebo-controlled trial to investigate benefits and harms of melatonin in medication-free children with rigorously diagnosed ADHD and SOI. Melatonin improved objective sleep onset and sleep duration, reduced subjective difficulty falling asleep, and induced advances of sleep onset of >30 minutes in about half of the melatonin-treated children. However, the findings did not support our initial hypothesis that melatonin treatment improved problem behavior, cognitive performance, or quality of life. Although parents reported an improvement in severity of individually defined core problems, this was mainly the result of an amelioration of problems related to sleep. Melatonin use was not associated with significant adverse events, which corresponds with previous randomized clinical trials in insomniac children (Dodge and Wilson, 2001; Jan et al., 1994; 2000; McArthur and Budden, 1998; O'Callaghan et al., 1999; Smits et al., 2001; 2003).

Melatonin advanced sleep onset (27 minutes) and DLMO (44 minutes) to normal values found previously in children with ADHD without insomnia (Van der Heijden et al., 2005b) or healthy children (Van der Heijden et al., 2005a). The present results corroborate our previous finding that delayed values of pretreatment DLMO are associated with more robust advancements of sleep-wake rhythm after melatonin treatment (Van der Heijden et al., 2005a). These findings suggest that melatonin synchronized circadian rhythms regulated by the biological clock. However, because we found that melatonin-induced changes in DLMO did not relate significantly to changes in sleep onset, it is likely that also direct soporific effects were involved in the improved sleep initiation (Sack et al., 1997; Van Someren, 2000).

In spite of improvements in sleep, melatonin demonstrated no effect on behavior, cognitive performance, and quality of life. We expected such improvements because sleep problems and sleep deprivation in children were associated with behavioral disturbances (Dahl, 1996; Sadeh et al., 2003). Furthermore, treatment of childhood insomnia showed improvements in health status (Smits et al., 2003), although this was not found for sustained attention (Smits et al., 2001). Possible explanations are that the present improvements in sleep were not large enough to induce improvements in behavior, cognitive performance, and quality of life; they may have required longer treatment duration; or they were possibly masked by large cognitive deficits found in children with ADHD.

The negative placebo effect on objective sleep measures was consistent with previous results in insomniac children (Smits et al., 2001; Van der Heijden et al., 2005a), but not with positive placebo effects usually found in adult insomniacs (Perlis et al., 2005). This is an interesting phenomenon for which we do not have a clear explanation.

The finding that no adverse events were reported in the placebo-treated group is unusual and may relate to the negative effects of placebo on sleep; namely, parents who experienced a worsening of the child's sleep problem assumed that their child received placebo, which may have caused a bias toward not perceiving or reporting adverse events.

Although we used pharmacological doses of 3 or 6 mg, previous studies in children used pharmacological doses of 2 to 12 mg, which were found to be safe and effective (Jan et al., 1994, 2000; McArthur and Budden, 1998; Smits et al., 2001, 2003). Physiological doses of melatonin (0.1, 0.3, and 1.0 mg) showed sleep-promoting effects in normal as well as insomniac adults (Almeida Montes et al., 2003; Zhdanova et al., 1995), but have not yet been studied adequately in children.

Strengths of the present study were the relatively large sample size, application of rigorous diagnostic methods and strict diagnostic criteria for ADHD as well as SOI, and stratified randomization to control for the effect of important factors. Furthermore, we used objective as well as subjective measures of sleep, behavior, cognitive performance, and quality of life and conducted a systematic 2-year follow-up of adverse events.

Limitations

Actigraphy is a well-validated instrument to evaluate sleep-wake rhythm over long periods in children (Littner et al., 2003); however, polysomnography assessments are required to evaluate sleep quality or sleep-related disorders such as periodic limb movement disorder and sleep-disordered breathing. Nevertheless, in the present study, reports of sleep disorder symptoms were rare and equally distributed over treatment groups, which reduces the risk that this factor affected the results. Furthermore, clinically relevant effects of melatonin on sleep quality are not expected (Almeida Montes et al., 2003). The number of missing data on some measures of behavior and quality of life was relatively large; however, the risk that a reporter bias distorted the data is small because the amount of missing data was equal in both treatment groups.

The present findings are likely generalizable to other ADHD populations because we recruited from heterogeneous health care settings, included all ADHD subtypes, and used diagnostic methods according to widely used psychiatric classification systems and practice guidelines. Our findings may not pertain to stimulant-treated children with ADHD because evidence suggests that stimulant treatment can deteriorate sleep (Ahmann et al., 1993; Stein, 1999). A double-blind, placebo-controlled trial in stimulant-treated children showed a reduction in sleep-onset insomnia of 16 minutes with melatonin compared to placebo (Weiss et al., 2006). An open-label study in stimulant-treated children showed robust advances of sleep onset (median, 135 minutes), without significant adverse events (Tjon Pian Gi et al., 2003).

Children with ADHD showed a greater night-to-night variability of sleep patterns compared with normal controls (Gruber et al., 2000). We found an interdaily stability of sleep-wake rhythm of 0.65 to 0.64, which was similar to the 0.63 found previously in children with ADHD without insomnia (Van der Heijden et al., 2005b), but was slightly lower than in children without ADHD or insomnia (0.68 ± 0.13; $n = 9$; unpublished results). It remains unknown whether this factor may have affected the present results.

Our criteria of SOI were based on a Dutch child population because international consensus criteria were not available. These criteria conformed to or were even stricter than recent consensus criteria for adult insomnia (American Academy of Sleep Medicine, 2001; Edinger et al., 2004). It remains unknown whether the current results also pertain to other cultures.

Clinical Implications

Melatonin induced clinically relevant advances of sleep onset and increased total time asleep in children with ADHD and SOI, with no apparent effects on behavior, cognition, and quality of life and with no significant adverse events. Nevertheless, we recommend that melatonin treatment be prescribed only when complaints of insomnia are persistent and severe and impose a burden on the individual child, if possible after amelioration of possible underlying extrinsic factors and preferably in those children demonstrating a delayed onset of endogenous melatonin rhythm. Systematic studies on possible long-term effects, such as on the gonadotropic system and onset of puberty (Luboshitzky and Lavie, 1999; Reiter, 1998) have not been conducted. Furthermore, melatonin has shown proconvulsant properties in children with epilepsy (Sheldon, 1998), although anticonvulsant effects were found as well (Peled et al., 2001). Previous studies including children younger than 6 years of age and adolescents demonstrated efficacy and safety of melatonin (Dodge and Wilson, 2001); however, rigorous trials in these specific age groups still must be conducted.

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