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A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities

Abstract: The purpose of this study was to determine the efficacy of controlled-release (CR) melatonin in the treatment of delayed sleep phase syndrome and impaired sleep maintenance of children with neurodevelopmental disabilities including autistic spectrum disorders. A randomized double-blind, placebo-controlled crossover trial of CR melatonin (5 mg) followed by a 3-month open-label study was conducted during which the dose was gradually increased until the therapy showed optimal beneficial effects. Sleep characteristics were measured by caregiver who completed somnologs and wrist actigraphs. Clinician rating of severity of the sleep disorder and improvement from baseline, along with caregiver ratings of global functioning and family stress were also obtained. Fifty-one children (age range 2–18 years) who did not respond to sleep hygiene intervention were enrolled. Fifty patients completed the crossover trial and 47 completed the open-label phase. Recordings of total night-time sleep and sleep latency showed significant improvement of approximately 30 min. Similarly, significant improvement was observed in clinician and parent ratings. There was additional improvement in the open-label somnolog measures of sleep efficiency and the longest sleep episode in the open-label phase. Overall, the therapy improved the sleep of 47 children and was effective in reducing family stress. Children with neurodevelopmental disabilities, who had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance, showed improvement in melatonin therapy.

Michael B. Wasdell[1], James E. Jan[1], Melissa M. Bomben[1], Roger D. Freeman[1], Wop J. Rietveld[2], Joseph Tai[1], Donald Hamilton[1] and Margaret D. Weiss[1]

[1]Melatonin Research Group, Department of Psychiatry, BC Children's Hospital, Vancouver, Canada; [2]Dutch Foundation for Chronobiology, Wassenaar, The Netherlands

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Address reprint requests to James E. Jan, Diagnostic Neurophysiology, BC Children's Hospital, 4500 Oak Street, Vancouver, BC, Canada V6H 3N1.
E-mail: jjan@cw.bc.ca

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Introduction

Children with neurodevelopmental disabilities (NDD) are at increased risk of having a sleep disorder [1, 2]. These tend to be longstanding, resistant to treatment and adversely affect development and health. Co-morbid sleep problems exacerbate the burden of NDD on caregivers [2]. A large proportion of these sleep difficulties are delayed sleep phase syndrome (DSPS) and impaired sleep maintenance (ISM). Sleep onset and maintenance are closely related on physiologic grounds and commonly occur together; therefore, we included both sleep disorders under the diagnosis of circadian rhythm sleep disorders (CRSDs) [3].

Campbell et al. describe CRSD as the misalignment between the endogenous clock that governs the timing of sleep and the sleep–wake cycle that is desired or which is regarded as the social norm [4]. CRSD is also defined as problems adapting to the light–dark cycle and inability to use cues which signal sleep (Zeitgebers). Children with special needs may have difficulties interpreting these signals such that their sleep patterns often deviate from the social norm [5]. There is evidence that inappropriately timed or deficient melatonin secretion is associated with persistent DSPS and ISM [5–9].

In 1994, melatonin therapy for children with NDD who had chronic sleep difficulties was introduced [10], and subsequent studies have demonstrated that it can be an effective treatment in this population with a benign short-term safety profile [6, 7, 11–19]. These and other studies have led to increasing acceptance of melatonin which is now being commonly prescribed as a first line of treatment [20, 21]. In all but two of these studies [6, 7], patient selection was based on the diagnosis of neurologic condition, rather than the diagnosis of the sleep disorder.

Two recent reviews, using meta-analysis of combined pediatric and adult studies concluded that melatonin therapy was ineffective for most sleep disorders with the exception of DSPS [22, 23]. A recent consensus statement on the pharmacologic management of insomnia in children and adolescents [2] concluded that studies on the safety and efficacy of pharmacologic treatment of insomnia were

urgently needed. Children with NDD, including autism spectrum disorders, who had co-morbid insomnia, were identified as the group with the highest priority because they had low response rates to other treatments. The consensus statement also suggested inclusion of measures of impact on family stress and functional gains.

Melatonin has many functions [24, 25]. Its administration may induce sleep during the day, when the endogenous levels of melatonin are low or absent [26]. In contrast, it does not yield additional sleep-promoting effect when the melatonin levels are adequate, even during the night [25]. We therefore hypothesize that this indoleamine selectively benefits those sleep disorders which are associated with an underlying nocturnal melatonin deficit, because melatonin drives the circadian rhythm [5, 25, 27].

Patients with NDD, especially when they are on multiple drugs, frequently have adverse events, many of which are related to the associated health problems. Demonstration of safety medication in this population requires expert clinical judgement as to whether or not a given adverse event is due to a medication or to the associated disorders [28]. Previous research has not included clinician analysis of adverse events.

Only one pediatric non-randomized clinical trial has utilized a controlled-release melatonin (CR-melatonin) formulation [29] and showed benefit to sleep maintenance. As in children with NDD there may be low endogenous melatonin secretion contributing to impairment in both the initiation of sleep and sleep maintenance, CR-melatonin may offer advantages over fast-release formulations. Thus, we conducted a placebo-controlled study of CR-melatonin treatment for DSPS and ISM in children with NDD as measured by parent, clinician, and objective report.

Materials and methods

Participants

Patients were recruited for the study by referral from pediatric psychiatrists and neurologists at British Columbia's Children's Hospital (Vancouver, Canada), a tertiary center serving the whole province. They were eligible to participate if they were between the ages of 2 and 18 yr, had multiple NDD and chronic DSPS or ISM (longer than 1.5 yr). Children were not eligible when their sleep difficulties were mild and not associated with daytime symptoms of insomnia (such as excessive drowsiness, inability to stay awake, lethargy, increased irritability and decreased functioning) and had progressive degenerative neurologic disorders, or life-threatening illnesses.

The sleep difficulty was confirmed by caregiver report and an evaluation of a 7-day sleep diary (somnolog) recorded by the child's caregivers. DSPS was characterized as a persistent nightly sleep onset delay of more than 30 min in relation to the desired time of sleep onset, with or without pre-sleep behavioral difficulties. ISM was defined by more than two prolonged awakenings lasting from 15 min up to several hours during the majority (70%) of nights and resulting in daytime symptoms of insomnia.

The study protocol was approved by the hospital scientific review board and the university ethics review board, and was carried out in accordance with the Declaration of Helsinki. Approval for the conduct of this trial was obtained from Health Canada. Prior to enrolment, oral and written study information was provided to each child's caregiver and informed consent was obtained.

Study design

The study was a randomized, placebo-controlled, double-blind, crossover trial of CR-melatonin (5 mg).

Intervention

Prior to randomization, there was a run-in period during which strict sleep hygiene designed according to patients' age, development, and individual disabilities was implemented. A pediatric nurse trained in sleep medicine, sleep hygiene, and neurologic disabilities supervised the caregivers. Patients, who continued to show disturbed DSPS and/or ISM in spite of sleep hygiene treatment, were randomized to receive CR-melatonin or placebo in the first phase of the crossover trial. The crossover trial consisted of 10 days of treatment (randomized by order – melatonin or placebo first), followed by a placebo washout for 3–5 days (to allow for weekends), followed by 10 days of the alternate treatment (melatonin or placebo second). Patients were randomly assigned by the hospital pharmacy to receive either melatonin or placebo first. A blocked randomization method was employed in which every four patients had equal probability of receiving either of the two treatment sequences. Patients, caregivers, study investigator, and clinical staff were blind to the medication randomization. Unblinding of the medication allocation for each patient occurred at the completion of the trial so that caregivers could make an informed decision as to whether or not they wished to continue treatment in the open-label study. Following the trial, patients continued in a 3-month open-label phase with bi-weekly telephone consultation and a final clinic visit where all outcome measures were repeated. Dose increments of 5 mg were permitted up to a maximum of 15 mg. An increase or decrease in the dose was permitted only following a discussion with the research team. As the caregivers understood their children the best, their requests were always carefully considered.

Study medication

Synthetic, pharmaceutical-grade melatonin 5 mg (provided by Circa Dia BV, The Netherlands) designed as a beaded sustained release (1 mg fast, 4 mg sustained release) and placebo was prepared by the hospital pharmacy in identical capsules and dispensed in a blister card containing the full medication supply. CR-melatonin 5 mg was chosen for this study based on previous research showing that it was an average effective dose [29, 30]. Caregivers were instructed to administer the study medication 20–30 min before the child's most desirable bedtime based on the baseline measurements and discussions between the caregivers and the team. Meals were avoided within 2–3 hr of administration.

Measures

Sleep characteristics

The primary outcome measure of efficacy was total night-time sleep as recorded on caregiver-completed somnologs, which provided a running record of the time when the child was asleep or awake during the relevant measurement period. Secondary outcome measures of sleep characteristics derived from the somnolog were sleep onset latency, sleep efficiency, longest sleep episode and number of night-time wakings. In addition, actigraph wrist-watches (Micro-Mini Motionlogger, Ambulatory Monitoring Inc., Ardsley, NY, USA) were worn nightly by patients on the non-dominant wrist. Actigraph measures of total night-time sleep, sleep onset latency, sleep efficiency, longest sleep episode and number of night-time wakings were summarized using the vendor's proprietary software. The reliability of actigraphy as a method for assessing sleep in children is well established [31]. The somnolog data were chosen over the actigraph data as the primary source of sleep measurement because it was anticipated that some of the patients with severe NDD would not be able tolerate wearing an actigraph.

Clinician and parent ratings

The Clinical Global Impression – Severity (CGI-S) and CGI – Improvement (CGI-I) [32] rating scales were used by the study physician to evaluate the effectiveness of treatment. The CGI-S provided a cross-sectional evaluation of the severity of the sleep difficulties on a seven-point scale ranging from 1 (normal) to 7 (among the most affected) at each visit. The CGI-I provided a longitudinal evaluation of improvement from baseline on a seven-point scale ranging from 1 (very much improved) to 7 (very much worse) for every visit following baseline.

Caregivers completed the Parents' Global Assessment Scale (PGAS), a variation of the CGI-S developed by the authors to capture the caregiver's perspective on the severity of the child's impairment across several functional and health dimensions. Ratings ranging from 1 (normal) to 7 (extremely severe) were assigned by the caregivers to eight individual items covering behavior, disposition, cognitive abilities and general health. Family stress due to the sleep disorder was rated on a four-point Family Stress Scale from 0 ('My family is not stressed') to 3 ('We can no longer cope, and we need immediate intervention') again at each visit.

Safety assessments were conducted at every visit. These assessments included open-ended interviews to document adverse events and evaluate their temporal and possible etiologic relationship to the study procedures and treatments (e.g., side effects), monitoring of concomitant medication use, brief physical examinations and evaluation of vital signs.

Sample size

The study aimed to detect a medium effect size of 0.40 with a power of 80% and a two-sided alpha of 0.05. Based on these calculations, a sample of 51 patients was determined to be sufficient.

Statistical analysis

Analysis of primary and secondary outcome measures was consistent with the analysis of crossover designs described by Senn [33]. To test the treatment effect, a *t*-test comparing the means of period differences in each of the two crossover sequences (melatonin then placebo versus placebo then melatonin) provided the estimate of the treatment effect that is adjusted for period differences. Carry-over and period effects were evaluated by unpaired *t*-tests comparing the mean period sums and the mean crossover differences of the two treatment sequences. For the open-label phase, paired *t*-tests comparing open-label somnolog measures with those obtained from the CR-melatonin treatment during the randomized trial were conducted to evaluate change over time. All statistical comparisons were performed using two-tailed tests at the 0.05 level of significance.

Results

Fifty-one children entered the randomized crossover trial which was conducted from September 2002 through May 2004. Fifty patients completed the trial as one patient withdrew from the study due to an acute illness. The mean age of the patients (31 males and 19 females) at baseline was 7.38 yr (range 2.05–17.81). CGI-S ratings at baseline indicated that all patients were at least 'moderately ill' (Table 1). Fifteen participants had been taking commercially available melatonin prior to the trial (ranging from 5 months to 9 yr). These patients discontinued their melatonin use 2 wk prior to the trial lead-in phase.

All children had more than one concurrent neurodevelopmental diagnosis such as severe intellectual loss (32), cerebral palsy (26), epilepsy (23), visual impairment (20), lack of mobility (18), and autism spectrum disorder (16). Medical chart review of neuroimaging (42) and electroencephalogram reports (46) identified diffuse brain damage in 18 patients, cerebral atrophy in 11, malformation in 7 and focal brain damage in 7 patients. Structural brain damage was not noted or suspected in 25 children.

Delayed sleep phase syndrome was noted in 32 cases and ISM in 34. DSPS alone was seen in 16 patients and 8 had sleep maintenance difficulties alone. With the exception of one individual, children who only had DSPS lacked diffuse structural brain damage. Children with ISM had diffuse bilateral brain damage (17), focal lesions (3), or no obvious abnormalities (14).

Baseline values of primary and secondary outcome measures are presented in Table 1. Validation of somnologs was given by a significant correlation between baseline somnolog and actigraph measures of total night-time sleep ($r = 0.72$, $P < 0.001$).

Fifty of the 51 patients completed the clinical trial and were included in the analysis. Observed values of outcome measures and results of statistical tests for treatment differences adjusting for period effects (*t*-tests of the period difference means) are summarized in Table 1. For the primary outcome measure of total night-time sleep by somnolog recording, improvement of approximately 31 min on CR-melatonin compared with placebo was

Table 1. Efficacy measures: baseline, crossover trial and period differences by treatment sequence

Outcome measure	Baseline	Crossover trial		Period differences by treatment sequence		P (analysis of period differences)
	No treatment	Placebo	Melatonin	Melatonin –placebo	Placebo–melatonin	
Somnolog						
Night-time sleep (min)	496.37 (71.06)	503.63 (87.72)	534.80 (86.22)	−37.00 (85.32)	24.54 (62.76)	< 0.01
Sleep latency (min)	72.87 (38.99)	65.18 (41.79)	32.48 (28.67)	24.83 (38.95)	−41.94 (43.99)	< 0.01
Longest sleep episode (min)	415.41 (106.23)	434.26 (109.09)	453.30 (118.41)	−27.33 (87.40)	9.30 (76.27)	0.12
Sleep efficiency (%)	93.84 (6.21)	94.72 (6.01)	94.95 (5.84)	0.49 (3.49)	1.08 (4.81)	0.62
Number of waking episodes	2.19 (1.34)	1.92 (0.95)	1.88 (1.23)	−0.05 (0.50)	−0.16 (0.70)	0.53
Actigraph						
Night-time sleep (min)	449.27 (92.29)	443.12 (79.98)	466.84 (91.08)	−26.40 (48.34)	20.35 (61.70)	< 0.01
Sleep latency (min)	76.59 (52.10)	66.79 (37.26)	42.53 (31.80)	15.99 (28.46)	−34.68 (45.86)	< 0.01
Longest sleep episode (min)	185.17 (102.63)	189.25 (99.98)	199.37 (100.46)	−27.33 (78.84)	−11.61 (92.96)	0.55
Sleep efficiency (%)	86.04 (9.59)	84.77 (10.63)	85.16 (8.96)	0.26 (7.00)	1.21 (7.60)	0.67
Number of waking episodes	12.08 (4.86)	11.38 (4.82)	11.83 (5.41)	−6.10 (3.04)	0.20 (4.35)	0.48
Clinical Global Impression						
Severity	4.52 (0.79)	4.42 (0.90)	3.16 (1.40)	1.04 (1.45)	−1.52 (1.38)	< 0.01
Improvement	4.10 (0.42)	4.30 (1.01)	2.36 (1.17)	2.11 (1.80)	−1.74 (1.74)	< 0.01
Parents' Global Assessment Scale	29.54 (7.96)	29.94 (8.14)	26.40 (8.45)	2.85 (5.63)	−4.35 (5.46)	< 0.01
Family stress	2.06 (0.61)	2.04 (0.35)	1.86 (0.45)	0.15 (0.60)	−0.22 (0.60)	< 0.05

Values are represented as mean (S.D.).

observed, and the test for treatment effect was significant ($P < 0.01$) and an effect size of 0.4.

Analysis of secondary outcome measures of sleep characteristics derived from somnologs (Table 1) showed significantly shorter sleep latency with CR-melatonin ($P < 0.01$). The effect size of the difference between CR-melatonin and placebo on sleep latency was 0.9. A similar pattern of results was observed in the analysis for treatment differences of the actigraph recordings where CR-melatonin treatment was associated with significantly longer total night-time sleep ($P < 0.01$) and shorter sleep latency ($P < 0.01$). Actigraph data were not obtained from seven patients who were not compliant with wearing the device. No other treatment differences were observed and there were no significant carry-over or period effects evident in any of the analyses.

Controlled-release melatonin produced improvements over placebo on both the CGI-S and CGI-I ratings. Mean CGI-S ratings during the placebo phase corresponded with 'moderate' severity whereas during the melatonin phase they were within the 'mild' severity range. The test for treatment differences was significant ($P < 0.01$). Similarly, the mean CGI-I rating with CR-melatonin treatment was significantly lower than that observed with placebo treatment ($P < 0.01$), and was associated with 'much' versus 'no' improvement of the sleep disorder from the baseline level, respectively. In both the PGAS and Family Stress scales, CR-melatonin treatment was associated with significantly lower parent-rated impairment ($P < 0.01$) and significantly lower family stress ratings ($P < 0.05$), respectively.

Treatment with CR-melatonin was well tolerated and no treatment differences were evident on vital signs or physical examinations. One serious adverse event, hospitalization because of aspiration pneumonia, occurred during placebo treatment in the first period of the crossover trial. This was consistent with this child's medical history and evaluated as not related to the study drug or procedures. This patient withdrew from the study.

Ninety-eight spontaneously reported treatment-emergent adverse events were documented: 36% in CR-melatonin, 40% in placebo and 24% in placebo washout phases. The most common adverse events among children receiving CR-melatonin were seizures (11), cold/flu/infection (8), gastro-intestinal illness (5), and agitation (4). There were two reports of anxiety and two reports of headache. These were consistent with the medical histories and were not considered to be related to CR-melatonin treatment. Forty percent of adverse events reported during CR-melatonin treatment originated from the same patient who had eight reports of seizures, four reports of agitation and one report each of gagging and headache. These events were consistent with the medical history of this patient.

Sixty-four percent of all treatment emergent adverse events were reported during the randomized placebo and placebo washout phases of the trial. Adverse events on randomized placebo were similar to those on CR-melatonin; there were reports of cold/flu/infection (10), seizures (8) and gastro-intestinal illness (5). There were seven reports of behavioral problems (e.g. agitation, anxiety, irritability, emotional lability). A similar pattern was seen in the placebo washout phase.

After the medication allocation was unblended, caregivers of all 50 subjects who completed the crossover trial volunteered to enter the open-label phase, but three children dropped out prior to completion (one child was given an unauthorized brand of melatonin, another was lost to follow-up, and the third child withdrew consent). The final doses noted in the open label were 5 mg for 21 patients, 10 mg for 25 patients, and 15 mg for 4 patients.

Somnolog measures were obtained after 3 months of open-label drug therapy for 46 patients. Significant improvement was observed in open label, longest sleep episode ($P < 0.05$) and sleep efficiency ($P < 0.01$) when

Table 2. Efficacy measures: randomized trial melatonin versus open-label melatonin

Outcome measure	Randomized trial (melatonin)	Open label (melatonin)	*P*-value
Somnolog (n = 46)			
Night-time sleep (min)	539.91 (83.38)	540.78 (86.72)	0.90
Sleep latency (min)	33.48 (29.45)	27.77 (24.97)	0.81
Longest sleep episode (min)	456.20 (120.86)	488.12 (122.69)	0.02
Sleep efficiency (%)	95.34 (5.18)	97.11 (4.52)	< 0.01
Number of waking episodes	1.83 (1.22)	1.50 (1.46)	0.10
Actigraph (n = 32)			
Night-time sleep (min)	461.76 (86.36)	434.69 (96.02)	0.08
Sleep latency (min)	44.07 (30.14)	46.49 (48.43)	0.80
Longest sleep episode (min)	174.15 (75.70)	174.29 (78.99)	0.99
Sleep efficiency (%)	84.45 (8.81)	86.74 (9.33)	0.10
Number of waking episodes	12.61 (5.63)	12.20 (5.37)	0.60
Clinical Global Impression (n = 46)			
Severity	3.04 (1.38)	2.24 (1.29)	< 0.01
Improvement	2.28 (1.17)	1.74 (1.06)	< 0.01
Parents' Global Assessment Scale	26.17 (8.64)	21.70 (11.85)	< 0.01
Family stress	1.89 (0.43)	1.65 (0.60)	0.01

Values are represented as mean (S.D.).

compared with melatonin treatment in the crossover trial (Table 2). No additional improvement at the last melatonin visit during the crossover study was seen in sleep latency, total night-time sleep and number of waking episodes. Valid actigraph data were obtained for only 32 patients from both the randomized melatonin and open-label periods. There was no further improvement in sleep latency or total night-time sleep in this subset of the original sample.

Open-label CGI-I ratings showed significantly greater improvement in the sleep disorder compared with the melatonin treatment of the randomized trial ($P < 0.01$; Table 2). Similarly, significantly milder clinician ratings of severity of sleep disorder were seen in open label ($P < 0.01$). Caregiver ratings of both severity and impact of sleep disorder on family stress also showed continued improvement with significantly lower ratings of severity being observed at the end of the open-label period than during the melatonin and placebo phases in the trial ($P < 0.01$ and $P < 0.05$), respectively).

There were no significant changes in the vital signs or physical examination at the end of the open-label phase. Only 18 adverse events were reported, all of which were consistent with pre-existing medical conditions. One serious adverse event occurred when a patient was hospitalized for upper respiratory infection for 3 days.

Post hoc analyses were conducted to evaluate the relationship between type of CRSD, extent of brain damage, and final dose in the open-label phase. Children with ISM had significantly greater representation of bilateral brain damage ($P < 0.01$) and their final open-label melatonin dose was also higher than in subjects with DSPS only ($P < 0.01$). Based on clinician evaluation of all measurements (sleep recordings, clinician, and parent ratings), melatonin benefited 47 children during the crossover trial or open-label follow-up.

Approximately 32% of patients in our sample had autistic spectrum disorders (n = 16). Because of the large representation of these patients and previous research interest in the treatment of sleep problems in these children [34, 35], post hoc analysis of this subsample was conducted to explore the potential efficacy of CR-melatonin treatment of CRSD in this patient population. DSPS was noted in 14 and ISM in 5 cases. CR-melatonin was effective in reducing sleep latency ($P < 0.01$) and promoting longer night-time sleep ($P < 0.01$).

Discussion

Our study showed that CR-melatonin was an effective treatment of DSPS and ISM in children with NDD, including autistic spectrum disorders. Evidence was provided that CR-melatonin benefited both sleep disorders with a mean increase in total sleep of 30 min. Improvement of the same magnitude in sleep onset latency was also observed. While it may appear that the increase in total night-time sleep can be explained by shortened sleep onset, the effect of reduced sleep latency should have resulted in a shifting of the sleep pattern rather than lengthening the sleep duration. Our findings are in contrast to the conclusions of the melatonin literature reviews using meta-analysis [22, 23] showing only an effect on sleep latency and not on sleep duration using short-acting melatonin. This difference is likely due to our use of CR-melatonin which may be acting both to initiate and maintain sleep. The methodology of this study allowed us to demonstrate that CR-melatonin treatment yielded improvement in how long it took the children to fall asleep, and how much sleep they obtained overall.

Analysis of patient variables revealed potential neurologic factors underlying melatonin response. Patients with DSPS only were less likely to have bilateral brain damage than those with ISM. This suggests that diffuse brain damage may predispose the child to ISM. Children and adults with acute or chronic bilateral brain damage frequently have low endogenous nocturnal melatonin secretion [36–42]. The rapid response to lower doses of melatonin for DSPS suggests that short-acting melatonin might be sufficient for these patients. In children with diffuse brain damage, the dose of melatonin was larger in

contrast to unilateral or absence of structural damage and the sleep response was slower and more variable. These patients may require higher than usual doses of melatonin. In this study, we prescribed variable pharmacologic doses. The selection of dose and formulation depends on multiple factors and a discussion of this complex topic is beyond the scope of this article.

Of the 50 patients who completed the trial, 47 benefited from melatonin therapy either during the randomized phase or the open-label follow-up. In three instances, melatonin had no effect: one patient had profound brain damage, another had chronic pain and in the third case, the parents failed to implement sleep hygiene. Scrutiny of the data indicated that withdrawal of melatonin among patients who were assigned to receive melatonin first in the randomized trial resulted in immediate return of sleep problems. This observation is supported by the lack of a statistically significant carryover effect. This quick relapse reflects the delayed onset of melatonin secretion reported in DSPS [6, 7], and low melatonin levels in ISM [5]. In contrast, there is a sustained effect of short-term melatonin therapy when used for jetlag which is associated only with temporary inappropriately timed melatonin secretion [24]. Thus our study supports the notion that melatonin therapy corrects an underlying physiologic deficit of this indoleamine in our patient sample.

Delayed sleep phase syndrome was often associated with anecdotal caregiver reports of disturbed pre-sleep behavior in the evening. Although this study did not include specific measures of behavior, whenever the sleep improved, parents reported diminished behavioral difficulties, which were even more evident in the open-label follow-up when sleep gains were consolidated. Anxiety was reported to be a problem for all children with autistic spectrum disorders. During the open-label phase, half of these patients had their dose increased that did not yield additional improvement in sleep latency or sleep duration, but caregivers spontaneously reported less anxiety. This anecdotal finding is consistent with research demonstrating the anxiolytic properties of melatonin [43, 44].

The consensus statement on sleep disorders called for controlled empirical studies of sleep problems in children with NDD that include measures from multiple informants and the impact of sleep problems on caregivers [2]. This is the first randomized placebo-controlled crossover study to demonstrate that the administration of CR-melatonin is a safe and effective means of initiating and maintaining sleep in children with NDD, even when they do not respond to strict sleep hygiene. In turn, improvement in sleep is associated with increased well-being for the family and the child. This finding is of particular importance in those patients who were selected for treatment on the basis of their sleep disorder, rather than the associated developmental disorder.

Even though our patient population was diverse, there was no evidence of side effects that were specific to CR-melatonin. Particularly, an increase in the severity and frequency of seizures and asthma, as suggested by some investigators [45, 46] was not observed. The effect of CR-melatonin was noted across clinician, parent, and actigraph measures, and continued to improve in follow up, rather than showing evidence of tolerance. These findings support the hypotheses that CR-melatonin benefits DSPS and ISM in children with NDD, including autistic spectrum disorders, because it corrects abnormally timed or reduced melatonin secretion.

The neurologic diagnoses in our sample of patients were highly variable, which is typical in any clinical sampling of special needs children. While we recognize the heterogeneity of neurologic problems in this sample, enrolment in the study was based on the type of sleep disorder which was the target of the melatonin therapy. Therefore, as long as the sleep disorders are similar, the variable neurologic diagnoses are not necessarily a limitation.

For practical reasons, we did not include blood or salivary melatonin level measurement. Obtaining melatonin levels in severely disabled children is a very difficult task, which would have interfered with their sleep, thus rendering our results less accurate. As our patient population frequently experienced ISM, sampling throughout the night would have been a great stressor and could have further disrupted already fragile sleep patterns. However, blood and saliva melatonin studies have already been done in individuals with a variety of neurologic disorders [8, 9, 42, 47–51]; therefore the lack of melatonin levels in our study is not a significant limitation. The results of this study showed a treatment effect of melatonin on sleep which suggests that there was deficiency of melatonin in our sample.

The primary outcome measure of efficacy was felt to be best measured by the caregiver-completed somnologs, although simultaneous actigraph recordings were also obtained. Both sleep measurements are valuable, but the actigraph offers more objective data. When they are done together, the two measurements complement each other. However, the data provided by somnolog and actigraph may differ due to the frequency of the recordings; somnolog recordings capture sleep status once every 15 min while actigraphs do so every minute. We correctly predicted that some children will not tolerate wearing actigraphs which justified the use of somnologs as the primary outcome measure.

Polysomnography is considered as the gold standard sleep measurement but young children and those with severe NDD frequently do not tolerate the procedure. However, CRSD can be accurately diagnosed by actigraphs and somnologs [52].

Satisfactory melatonin dose studies have not been performed in children. A review of the literature showed that the average dose used for disabled children with sleep disorders is 2–10 mg [29]. The 5 mg tablets used in the study were effective, but it is possible that a lower dose would have yielded similar results. It will be important for dose studies to be conducted in the future.

Sleep hygiene was used as a pretreatment prior to randomization. For children with NDD, sleep hygiene needs to be designed on individual bases because it is strongly influenced by the type of neurologic deficit and by the child's environment. The individual tailoring of a sleep hygiene intervention may be viewed as a limiting factor in this study. However, a standardized sleep hygiene intervention might have failed for some children who would have otherwise responded to a customized program.

Sleep in normally developed children may be disrupted temporarily by changes in health. In children with NDD, disruptions in sleep patters may occur more frequently as a consequence of their disorders. It is noted that the study procedures contained relatively short periods of sleep recordings (i.e. 7–10 days) with a rigid schedule of study visits and could not accommodate postponement of assessments of patients who had become acutely ill during the course of the study. It is recommended for future research of sleep in children with NDD that there be flexibility of study schedules and/or longer periods of sleep measurements.

Disclosure

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References

1. Turk J. Melatonin supplementation for severe and intractable sleep disturbance in young people with genetically determined developmental disabilities: short review and commentary. J Med Genet 2003; **40**:793–796.
2. Mindell JA, Emslie G, Blumer J et al. Pharmacologic management of insomnia in children and adolescents: consensus statement. Pediatrics 2006; **117**:e1223–e1232.
3. Scher MS. Applying classifications of sleep disorders to children with neurologic conditions. J Child Neurol 1998; **13**:525–536.
4. Campbell SS, Murphy PJ, Van Den Heuvel CJ et al. Etiology and treatment of intrinsic circadian rhythm sleep disorders. Sleep Med Rev 1999; **3**:179–200.
5. Jan JE, Freeman RD. Melatonin therapy for circadian rhythm sleep disorders in children with multiple disabilities: what have we learned in the last decade? Dev Med Child Neurol 2004; **46**:776–782.
6. Smits MG, Nagtegaal EE, Van Derheijden K et al. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol 2001; **16**:86–92.
7. Smits MG, Van Stel HF, Van Der Heijden K et al. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 2003; **42**:1286–1293.
8. Potocki L, Glaze D, Tan DX et al. Circadian rhythm abnormalities of melatonin in Smith–Magenis syndrome. J Med Genet 2000; **37**:428–433.
9. Jan JE, Wasdell MB, Reiter RJ et al. Melatonin therapy of pediatric sleep disorders: Recent advances, why it works, who are the candidates and how to treat. Curr Pediatric Rev 2007; **3**:214–224.
10. Jan JE, Espezel H, Appleton RE. The treatment of sleep disorders with melatonin. Dev Med Child Neurol 1994; **36**:97–107.
11. Jan JE, O'donnell ME. Use of melatonin in the treatment of paediatric sleep disorders. J Pineal Res 1996; **21**:193–199.
12. Mcarthur AJ, Budden SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. Dev Med Child Neurol 1998; **40**:186–192.
13. O'callaghan FJ, Clarke AA, Hancock E et al. Use of melatonin to treat sleep disorders in tuberous sclerosis. Dev Med Child Neurol 1999; **41**:123–126.
14. Dodge NN, Wilson GA. Melatonin for treatment of sleep disorders in children with developmental disabilities. J Child Neurol 2001; **16**:581–584.
15. Niederhofer H, Staen W, Mair A et al. Brief report: melatonin facilitates sleep in individuals with mental retardation and insomnia. J Autism Dev Disord 2003; **33**:469–472.
16. Coppola G, Iervolino G, Mastrosimone M et al. Melatonin in wake–sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. Brain Dev 2004; **26**:373–376.
17. Gupta M, Gupta YK, Agarwal S et al. Effects of add-on melatonin administration on antioxidant enzymes in children with epilepsy taking carbamazepine monotherapy: a randomized, double-blind, placebo-controlled trial. Epilepsia 2004; **45**:1636–1639.
18. Hancock E, O'callaghan F, Osborne JP. Effect of melatonin dosage on sleep disorder in tuberous sclerosis complex. J Child Neurol 2005; **20**:78–80.
19. Siegrist C, Benedetti C, Orlando A et al. Lack of changes in serum prolactin, FSH, TSH, and estradiol after melatonin treatment in doses that improve sleep and reduce benzodiazepine consumption in sleep-disturbed, middle-aged, and elderly patients. J Pineal Res 2001; **30**:34–42.
20. Owens JA, Rosen CL, Mindell JA. Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians. Pediatrics 2003; **111**:e628–e635.
21. Clark AF. Incidences of new prescribing by British child and adolescent psychiatrists: a prospective study over 12 months. J Psychopharmacol 2004; **18**:115–120.
22. Buscemi N, Vandermeer B, Hooton N et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med 2005; **20**:1151–1158.
23. Buscemi N, Vandermeer B, Hooton N et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Br Med J 2006; **332**:385–393.
24. Arendt J, Skene DJ. Melatonin as a chronobiotic. Sleep Med Rev 2005; **9**:25–39.
25. Zhdanova IV. Melatonin as a hypnotic: Pro. Sleep Med Rev 2005; **9**:51–65.
26. Smith MR, Lee C, Crowley SJ et al. Morning melatonin has limited benefit as a soporific for daytime sleep after night work. Chronobiol Int 2005; **22**:873–888.
27. Palm L, Hellsten H. Sleep disorders in healthy children follows often a "learnt" behavioral pattern. Diurnal rhythm

disturbances are dominating among children with functional disabilities. Lakartidningen 1999; **96**:5200–5206.
28. Carleton BC, Smith MA, Gelin MN et al. Paediatric adverse drug reaction reporting: understanding and future directions. Can J Clin Pharmacol 2007; **14**:e45–e57.
29. Jan JE, Hamilton D, Seward N et al. Clinical trials of controlled-release melatonin in children with sleep–wake cycle disorders. J Pineal Res 2000; **29**:34–39.
30. Jan JE, Freeman RD, Fast DK. Melatonin treatment of sleep–wake cycle disorders in children and adolescents. Dev Med Child Neurol 1999; **41**:491–500.
31. Laakso ML, Leinonen L, Lindblom N et al. Wrist actigraphy in estimation of sleep and wake in intellectually disabled subjects with motor handicaps. Sleep Med 2004; **5**:541–550.
32. NIMH CGI (Clinical Global Impression Scale) – NIMH. Psychopharmacol Bull 1985; **21**:839–844.
33. Senn SJ. Cross-over Trials in Clinical Research.Wiley, Chichester, 2002.
34. Patzold LM, Richdale AL, Tonge BJ. An investigation into sleep characteristics of children with autism and Asperger's Disorder. J Paediatr Child Health 1998; **34**:528–533.
35. Richdale AL, Prior MR. The sleep/wake rhythm in children with autism. Eur Child Adolesc Psychiatry 1995; **4**:175–186.
36. Pang SF, Li Y, Jiang DH et al. Acute cerebral hemorrhage changes the nocturnal surge of plasma melatonin in humans. J Pineal Res 1990; **9**:193–208.
37. Zhdanova IV, Wurtman RJ, Lynch HJ et al. Sleep-inducing effects of low doses of melatonin ingested in the evening. Clin Pharmacol Ther 1995; **57**:552–558.
38. Heikkila E, Hatonen TH, Telakivi T et al. Circadian rhythm studies in neuronal ceroid-lipofuscinosis (NCL). Am J Med Genet 1995; **57**:229–234.
39. Bazil CW, Short D, Crispin D et al. Patients with intractable epilepsy have low melatonin, which increases following seizures. Neurology 2000; **55**:1746–1748.
40. Sivan Y, Laudon M, Kuint J et al. Low melatonin production in infants with a life-threatening event. Dev Med Child Neurol 2000; **42**:487–491.
41. Moskala M, Krupa M, Goscinski I et al. Circadian rhythms of melatonin of patients with severe traumatic brain injury. Neurol Neurochir Pol 2004; **38**:401–404.
42. Tordjman S, Anderson GM, Pichard N et al. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. Biol Psychiatry 2005; **57**:134–138.
43. Golombek DA, Pevet P, Cardinali DP. Melatonin effects on behavior: possible mediation by the central GABAergic system. Neurosci Biobehav Rev 1996; **20**:403–412.
44. Zhdanova IV, Piotrovskaya VR. Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans. Pharmacol Biochem Behav 2000; **67**:131–135.
45. Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. Lancet 1998; **351**: p. 1254.
46. Sutherland ER, Martin RJ, Ellison MC et al. Immunomodulatory effects of melatonin in asthma. Am J Respir Crit Care Med 2002; **166**:1055–1061.
47. Laakso ML, Leinonen L, Hatonen T et al. Melatonin, cortisol and body temperature rhythms in Lennox–Gastaut patients with or without circadian rhythm sleep disorders. J Neurol 1993; **240**:410–416.
48. Miyamoto A, Oki J, Takahashi S et al. Serum melatonin kinetics and long-term melatonin treatment for sleep disorders in Rett syndrome. Brain Dev 1999; **21**:59–62.
49. Palm L, Blennow G, Wetterberg L. Long-term melatonin treatment in blind children and young adults with circadian sleep–wake disturbances. Dev Med Child Neurol 1997; **39**:319–325.
50. Guerrero JM, Pozo D, Diaz-Rodriguez JL et al. Impairment of the melatonin rhythm in children with Sanfilippo syndrome. J Pineal Res 2006; **40**:192–193.
51. Paparrigopoulos T, Melissaki A, Tsekou H et al. Melatonin secretion after head injury: a pilot study. Brain Inj 2006; **20**:873–878.
52. Ancoli-Israel S, Cole R, Alessi C et al. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003; **26**:342–392.