Original Article

Melatonin for Chronic Sleep Onset Insomnia in Children: A Randomized Placebo-Controlled Trial

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ABSTRACT

To establish the efficacy of melatonin treatment in childhood sleep onset insomnia, 40 elementary school children, 6 to 12 years of age, who suffered more than 1 year from chronic sleep onset insomnia, were studied in a double-blind, placebo-controlled study. The children were randomly assigned to receive either 5-mg melatonin or placebo. The study consisted of a 1-week baseline, consecutively followed by a 4-week treatment period. After that period, treatment was continued if the parents wished so. The study's impact was assessed by measurements of lights-off time, sleep onset, and wake-up time, recorded in a diary (n = 33). Sleep onset was also recorded with an actigraph (n = 25). Endogenous dim light melatonin onset was measured in saliva (n = 27). Sustained attention was evaluated with the Bourdon-Vos reaction time test (n = 36). In the melatonin group, mean (95% CI) lights-off time advanced 34 (6–63) minutes, diary sleep onset 63 (32–94) minutes, actigraphic sleep onset 75 (36–114) minutes, and melatonin onset 57 (24 to 89) minutes; total sleep time increased 41 (19–62) minutes. In the placebo group, these parameters did not shift significantly. The change during the 4-week treatment period differed between the treatment groups significantly as to lights-off time, diary and actigraphic sleep onset, sleep duration, and melatonin onset. There were no significant differences between the treatment groups in the change of sleep latency, wake-up time, and sustained attention reaction times. Mild headache occurred in 2 children during the first 2 days of the melatonin treatment. Eighteen months after the start of the trial, in 13 of the 38 children who could be followed up, melatonin treatment was stopped because their sleep problem was solved and in 1 child because sleep was not improved. Twelve children used melatonin 5 mg, the other 1.0 to 2.5 mg. One child developed mild generalized epilepsy 4 months after the start of the trial. The results show that melatonin, 5 mg at 6 PM, was relatively safe to take in the short term and significantly more effective than placebo in advancing sleep onset and dim light melatonin onset and increasing sleep duration in elementary school children with chronic sleep onset insomnia. Sustained attention was not affected. (*J Child Neurol* 2001;16:86–92).

Chronic sleep onset insomnia occurs in about 10% of the nondisabled school-aged population[1] and is associated with increased occurrence of fears, night wakening, difficulty getting up in the morning, and daytime fatigue. Consequently, it may induce various cognitive and behavioral problems in children, as well as more widespread difficulties in their families.[1-3] To avert sleep onset delays, parents are advised to take sleep hygiene improving measures such as fixed bedtime routines, a quiet bedroom, a warm bath before going to bed, physical affection (eg, hugs and kisses), and avoiding watching exciting movies before going to sleep.[4,5] When these nonpharmacologic measures are unsuccessful, antihistamines, benzodiazepines, and neuroleptics are currently prescribed. Although helpful, they are poorly studied in children and may cause confusion, morning sedation, and long-term adverse effects.[6]

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Children who display delayed sleep onset and bedtime resistance may also wake up later.[1] This suggests that their sleep-wake rhythm is delayed.[1]

Endogenous melatonin, a hormone produced by the pineal gland during the dark phase of the day-night cycle, plays a major role in the synchronization of circadian rhythms.[7] As early as the second half of the first year of life, melatonin is involved in the evolution of the sleep-wake system.[8] The circadian rhythm of melatonin is highly reproducible and generally not easily altered.[9] The endogenous 24-hour melatonin profile is a reliable marker for circadian phase position. To assess differences in circadian phase position, it is not necessary to measure the complete 24-hour profile. The time at which melatonin starts to rise in dim light, the dim light melatonin onset, is shown to be particularly convenient, as it can usually be obtained before sleep.[10]

In adults with chronic sleep onset insomnia and a delayed sleep-wake rhythm, melatonin, 5 mg, advances both sleep onset and melatonin onset.[11] In children, melatonin treatment has been studied in a few, mostly uncontrolled, trials. These studies were related to blind and mentally handicapped children with chronic insomnia and sleep disturbances due to fragmented sleep. They reported mixed findings about efficacy.[12-15] It is not known whether pharmacokinetic and side effects of melatonin in children differ from those in adults. Therefore, it is necessary to study these aspects in children, too.[16]

We hypothesized that exogenous melatonin advances both sleep and endogenous melatonin onset in children with chronic sleep onset insomnia. Therefore, we conducted a randomized, double-blind, placebo-controlled, parallel-group trial in elementary school children with chronic sleep onset insomnia.

METHODS

The trial was conducted between April 1997 and May 1998. From June until September, children were not included in the trial because they have holidays during this period and consequently their sleep-wake rhythm may be irregular. Elementary school children with chronic sleep onset insomnia were referred to our sleep center by local pediatricians and child psychologists. Eligible participants were those children aged between 6 and 12 years, who were in general good health. Sleep onset insomnia was defined as sleep onset later than 8:30 PM in children aged 6 years and for older children 15 minutes later per year until age 12 years. Furthermore, the latency between lights-off time and sleep onset (sleep latency) had to be more than 30 minutes. We included the children, based on the parental reports, when they suffered from sleep onset insomnia more than 4 nights a week, during more than 1 year before the start of the trial, and sleep onset did not advance sufficiently with the usual sleep hygiene improving measures.[4] Exclusion criteria were disturbed sleep architecture measured by ambulatory polysomnography with 24-hour cassette electroencephalography at the child's home: sleep maintenance insomnia (one awakening > 30 minutes or two or more awakenings of > 5 min-

utes summing up to at least 40 minutes, occurring on 1 or more nights a week, for a period of at least 4 weeks preceding the start of the trial[17]); mental handicap; severe learning disabilities; any prior use of melatonin; liver diseases; renal failure; use of hypnotics, antidepressants, and neuroleptics; chronic pain; and severe neurologic or psychiatric disorders. At enrolment, children were examined by a neurologist (MGS) who specializes in childhood sleep disorders, minimizing the possibility that chronic sleep onset insomnia was due to habits and associations, poor limit settings, fears, improper schedules, medical triggers, and neurologic dysfunction.[18] The trial consisted of two consecutive periods: a 1-week qualification period, during which baseline sleep, melatonin, and performance parameters were assessed, and 4 weeks of treatment, during which participants were randomly allocated to melatonin or placebo therapy. During the fourth treatment week, effects on sleep, melatonin, and performance were assessed. To see whether the children chose to go to bed earlier on their own accord, during the trial, the children were allowed to go to bed when they felt tired rather than at a scheduled sleep time. They were not allowed to change their comedication.

Patients were randomized in blocks of 10 to keep possible time effects to a minimum. All investigators involved in the study were unaware of the treatment allocation. The code was broken when the data of all patients were recorded in the database of the Statistical Package for the Social Sciences (SPSS). The trial was conducted according to the European Guidelines for Good Clinical Research Practice in children[19] and followed the 1983 revised provisions of the 1975 Declaration of Helsinki. The local Medical Ethical Committee approved the protocol. The participants' parents gave written informed consent to take part. They knew that their children could receive, if they wished, "open" melatonin, 5 mg, immediately after finishing the fourth treatment week.

Sleep
During the baseline and the fourth treatment week, the parents recorded lights-off time, sleep onset, and wake-up time daily in a diary. Sleep latency and the total sleep time were estimated. Mean values of the first 4 consecutive nights of the baseline and fourth treatment week were computed. At the third and fourth nights of the baseline and fourth treatment week, sleep onset was measured with an actigraph (Gähwiler Electronics, Hombrechtikon, Switzerland). The children wore this motion-sensing device, the size of a matchbox, attached to the nondominant wrist, from 6 PM until 8:00 AM. Actigraphic monitoring measures movements in 30-second periods. Sleep onset, as derived from the wrist activity records and averaged over the 2 nights, was estimated as described elsewhere.[20]

Dim Light Melatonin Onset
At the last nights of the baseline and the fourth treatment week, salivary samples were collected hourly from 7 to 11 PM by chewing on a cotton plug (Salivetten, Sarstedt Nümbrecht, Germany) for 1 minute. We chose that time because earlier studies[11,21] showed that melatonin onset could be expected to occur in that time range. Salivary melatonin concentrations were measured as described elsewhere.[22] To prevent suppression of melatonin secretion by bright light,[23] the children remained in their beds during that period while the curtains were closed. Dim light was allowed. Dim light melatonin

onset, defined as the time at which salivary melatonin reached 4 pg/mL, was calculated as the linearly interpolated time of the first sample above 4 pg/mL that was preceded by a lower value.[22,24] In the fourth treatment week, the children did not take the study medication during the night of saliva collection.

Sustained Attention

Sustained attention was measured at day 4 or 5 of the baseline and fourth treatment week with the Bourdon-Vos test.[25] As we found that melatonin treatment makes patients feel more refreshed in the morning,[11] we hypothesized that melatonin treatment would improve sustained attention particularly at that time of the day. Because of this, sustained attention was measured between 10 and 12 AM. The Bourdon-Vos test has been validated to assess sustained attention and regularity in performance in Dutch people.[25] It is a frequently applied cancellation test in which 33 rows of 24 small patterns of three, four, or five dots are presented. The four-dot patterns are the targets. The subject must cancel the targets in normal reading order, as fast and as accurately as possible. The test lasts about 10 minutes. The experimenter registers on-line the successive row completion time. This time decreases with age in an exponential fashion from 22.3 seconds for 6-year-old children to 10.3 seconds for 17-year-old youngsters. Accuracy, measured in (1) terms of omissions (missed targets), (2) corrections (immediately noticed cancellations of nontargets), and (3) errors (cancelled nontargets), appears to be a personal, age-invariant factor. Norms for row completion time and for each of the three features of accuracy have been established for the age groups from 6- to 18-year-old subjects.[25] In the present study, test results were divided into three consecutive blocks of equal time. Mean row completion time, omissions, corrections, and errors of these three blocks were computed.

Treatment

Participants received at 6 PM 5-mg melatonin (Helsinn Chemicals SA, Biasca, Switzerland) orally, mixed with lactose in a fast-release tablet, or an identically looking matched placebo. Compliance was tested by comparison of the number of tablets returned with the number prescribed.

Outcome Measures

The primary outcome measures were the between-group differences in the mean change from baseline to week 4, including lights-off time, sleep latency, sleep onset, sleep duration, wake-up time, dim light melatonin onset, reaction times, and number of omissions, corrections, and errors. The parents were encouraged to describe any suspected adverse effects in the diary.

Statistical Analysis

We calculated our sample size on the basis of data from our studies in adults with chronic sleep onset insomnia and delayed sleep-wake rhythm.[11,21] We estimated that 12 participants were required in each treatment group to give a power of 90% and a significance level of .05 in detecting a between-group difference of at least 60 (± 45) minutes as to sleep onset and dim light melatonin onset. We expected that in each group, 8 children or their parents would not complete all of the tests. Therefore, we included 20 children in each group of the trial.
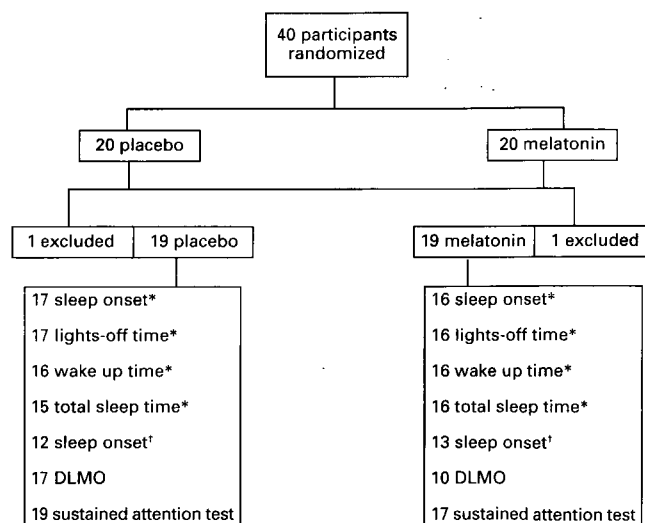

Figure 1.   Trial profile. *Diary; †actigraphy. DLMO = dim light melatonin onset.

The intergroup differences at the baseline week were analyzed with chi-square and Student's t-test. A P value of less than .05 was considered significant. Equality of variances was investigated with Levene's test. When variances were equal, pooled variance was used in the calculation of the results of the t-test. When variances were unequal, separate variance estimates were used. The differences between placebo and melatonin treatment groups in the change during the 4-week treatment period were analyzed with an analysis of variance (ANOVA) repeated-measures procedure with treatment (placebo versus melatonin) as a between-subjects factor and measurement (baseline versus fourth treatment week) as a within-subjects factor. To establish whether the use of methylphenidate or gender influenced the results, these features were subsequently used as cofactors. Because of potential inhomogeneity of variances and covariances, the degrees of freedom were corrected by using the Huynh-Feldt procedure. Significant treatment × measurement interactions, indicating a differential treatment effect across groups, were followed by post hoc comparisons of the baseline with treatment measurements, using paired t-test; the between-group differences in the mean change from baseline to fourth treatment week were analyzed using t-test. Correlations between sleep parameters, dim light melatonin onset, and sustained attention tests were analyzed by Pearson correlation. The trend of the reaction times was analyzed with orthogonal polynomial trend analysis.

RESULTS

Forty children, 28 boys and 12 girls, entered the trial (Figure 1). Ages and mean diary sleep onset at baseline are presented in Figure 2. Twenty children were randomly assigned to melatonin and 20 to placebo treatment. One boy of the placebo group was withdrawn because of an allergic reaction to lactose in the medication and one girl of the melatonin group because her parents withdrew their informed consent after randomization. The melatonin group consisted
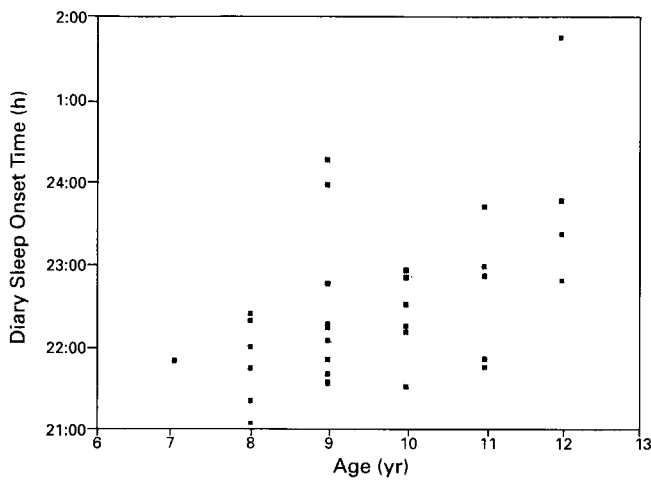
Figure 2. Baseline mean diary sleep onset and age of the study population.

of 11 boys and 8 girls; the mean age was 10.3 (SD 1.6) years. Two children used salbutamol (inhalor) as needed for asthma. Five boys used methylphenidate (10–25 mg daily) for attention-deficit hyperactivity disorder (ADHD). The placebo group consisted of 16 boys and 3 girls; the mean age was 9.3 (SD 1.5) years. One child used lactitol for chronic constipation. Six boys used methylphenidate (10–30 mg) for ADHD. In the children who used methylphenidate, sleep onset insomnia was present more than 1 year before the start of the methylphenidate.

The parents of five children did not complete the diaries. Eleven children forgot to produce saliva for determining melatonin levels or took by mistake the trial medication at the night at which saliva was collected. Because of technical problems, the actometer data of 13 children could not be analyzed. Two children did not complete the Bourdon-Vos test. Age, sex distribution, mean sleep characteristics, dim light melatonin onset, and sustained attention reaction times at baseline did not differ between the placebo and melatonin groups (Table 1). Compliance was good (> 98% pills taken).

As shown in Table 1, ANOVA showed significant treatment × measurement interactions for lights-off time, diary and actigraphic sleep onset, sleep duration, and dim light melatonin onset. Post hoc analysis showed that in the melatonin group, lights-off time, dim light melatonin onset, and diary and actigraphic sleep onset advanced and total sleep time increased in the fourth treatment week (P values, respectively: .034, <.001, .005, .006, and .035). These parameters did not change significantly in the placebo group (P values, respectively: .936, .123, .083, .211, and .744).

In the placebo group, diary and actigraphic sleep onset did not correlate at baseline or in the fourth treatment week. In the melatonin group, this correlation increased from 0.51 (P = .11) at baseline to 0.68 (P = .02) in the fourth treatment week.

In the baseline week, dim light melatonin onset correlated moderately with diary (0.47; P = .016) and actigraphic sleep onset (0.48; P = .033) when calculated over all participants. When the data of the melatonin and the placebo group were analyzed separately, both at baseline and in the fourth treatment week, dim light melatonin onset and sleep onset (diary and actigraphy) did not correlate.

The differences in the mean change of the row completion time (see Table 1) and the other Bourdon-Vos test parameters from baseline to week 4 were not significant between the treatment groups. The trend of the reaction times, omissions, corrections, and errors had not changed significantly during melatonin treatment compared with placebo treatment. Bourdon-Vos test results, sleep parameters, and dim light melatonin onset did not correlate.

From the covariance analysis, it appeared that neither gender nor the use of methylphenidate significantly influenced sleep parameters, dim light melatonin onset, and sustained attention test outcomes.

Mild transient headache occurred during the first two days of melatonin treatment in two children.

Immediately after the trial, all participants received "open" melatonin, 5 mg at 6 PM. At follow-up visits, scheduled every 3 months, the parents were encouraged to lower the dose and to stop treatment on vacations. In October 1998, 18 months after the start of the trial, the effects of melatonin treatment were evaluated with a written questionnaire,

Table 1.   Mean (SD) Sleep Parameters, Dim Light Melatonin Onset, and
Bourdon-Vos Test Row Completion Time at Baseline and Fourth Treatment Week

	Baseline			Fourth Treatment Week		Treatment Interaction			
	Melatonin	Placebo	P Difference	Melatonin	Placebo	F	DF	E	P
Lights-off time* (min)	9:42 PM (0:56)	9:10 PM (0:47)	.09	9:07 PM (0:55)	9:02 PM (0:36)	4.9	29	1	.035
Sleep onset* (min)	10:45 PM (1:07)	10:13 PM (0:43)	.11	9:42 PM (1:15)	9:59 PM (0:37)	9.4	31	1	.005
Sleep latency* (min)	62.9 (30.5)	61.7 (32.3)	.91	34.5 (29.8)	49.6 (33.3)	2.4	32	1	.128
Wake-up time* (min)	7:46 AM (0:45)	7:23 AM (0:25)	.09	7:22 AM (0:24)	7:21 AM (0:48)	2.3	30	1	.144
Total sleep time* (min)	9:03 (0:39)	9:10 (0:31)	.58	9:43 (0:44)	9:14 (0:49)	5.5	29	1	.026
Sleep onset[†] (min)	10:16 PM (1:32)	9:21 PM (0:42)	.06	9:09 PM (1:15)	10:06 PM (1:48)	9.9	23	1	.005
Dim light melatonin onset (min)	9:10 PM (1:54)	9:03 PM (0:39)	.82	9:33 PM (0:57)	9:36 PM (1:15)	9.9	25	1	.004
Row completion time (sec)	16.3 (3.3)	17.5 (3.6)	.33	13.7 (2.3)	15.6 (3.5)	0.8	31	1	.390

*Diary; [†]actigraphy.

Treatment interaction: ANOVA with repeated-measures statistics. F = F ratio; DF = degrees of freedom of error (baseline versus fourth treatment week); E = Epsilon Huynhl-Feldt procedure correction; P = level of significance.

answered by 33 parents. The remaining 5 parents were interviewed by telephone. At that time, treatment was stopped in 14 children, in one child because sleep onset had not advanced enough and in the other 13 because their sleep problem was solved. Their mean treatment period was 7.7 (4.3) months (range 2–14 months). The other 24 children still received melatonin. Their mean treatment period was 11.9 (SD 4.7) months (range 5–19 months). Mean time of intake was 7:10 PM (SD 0:47) (range 6–8:30 PM). In 12 children, the dose was reduced to 1.0 to 2.5 mg; 12 children still used 5 mg. In 6 of these 12 children, the dose had been reduced to 2.5 mg. Because their sleep onset was delayed, the dose was increased again to 5 mg. One boy developed mild generalized epilepsy 4 months after the start of the melatonin treatment. Because sleep had improved, the parents refused to stop melatonin treatment. So we decided to continue the melatonin and to add valproate, 500 mg daily. From that time, seizures did not recur.

Many parents enthusiastically indicated that their child's behavior had considerably improved within a few months of treatment. They did not report deterioration of sleep quality.

DISCUSSION

The present study showed that 1-month melatonin treatment advanced mean lights-off time, sleep onset, and melatonin onset and increased mean sleep duration in children with chronic sleep onset insomnia. Sustained attention was not affected, and serious side effects did not occur.

The freedom for the children to go to bed and sleep when they felt tired can explain why mean sleep latency did not change, whereas sleep onset and lights-off time advanced.

The poor correlation between diary and actigraphic sleep onset, found in our study, is in accordance with the poor correlation between parental report, child report, and automated measurement of children's sleep reported in earlier studies.[1] Recently, Acebo et al[26] showed that 5 or more nights of usable actigraphic registrations are required to obtain reliable measures of sleep.[26]

As normal values of dim light melatonin onset in 6- to 12-year-old children have not been published, it is not known whether the mean baseline melatonin onset, which occurred in our group of children at 9:10 PM, is abnormal. However, Carskadon et al[24] found that mean melatonin onset occurs at 8:24 PM in 14-year-old healthy adolescents. One year later, this value was delayed about 40 minutes. So the melatonin onset that we found probably is later than what might be expected. This late value suggests that in our children with chronic sleep onset insomnia the endogenous circadian pacemaker is delayed.[10] This can be due to dysfunction of clock genes,[27,28] enzymes involved in the melatonin synthesis,[11] or neural connections between the retina and pineal gland.[29]

In healthy subjects, melatonin onset correlates reasonably with sleep onset.[30] We found only a weak correlation in

our children with chronic sleep onset insomnia. This could be due to the sleep problem (ie, a disregulation of the timing of sleep). The advancement of the melatonin onset reported in our study is in accordance with earlier findings showing that melatonin advances the rising slope of the melatonin curve in adults with chronic insomnia and delayed sleep-wake rhythm.[11] This suggests that melatonin treatment had advanced the phase of the endogenous circadian pacemaker.[10]

The delayed sleep onset and the late melatonin onset, characteristics of delayed sleep phase syndrome,[11] suggest that the children in our study suffered from this circadian rhythm disorder. Although the delayed sleep phase syndrome often originates in childhood, sleep studies of children with delayed sleep phase syndrome have not been reported. So, we could not prove this disorder in our group. Difficulty arising in the morning at conventional times, one of the characteristics of the delayed sleep phase syndrome, might have been masked in the children by extrinsic factors in the family or intrinsic factors, such as hyperarousal conditions, associated with ADHD.[2] Nevertheless, in future studies, it might be worthwhile to compare sleep time during weekends with sleep time during schooldays in children suspected of a circadian rhythm disorder. When the diagnostic value of the dim light melatonin onset in adult and childhood delayed sleep phase syndrome has been established, sleep onset insomnia, caused by sleep phase delay, possibly can be distinguished more easily from sleep onset insomnia due to other causes.

Even though melatonin treatment increased mean total sleep time about 40 minutes in our study, sustained attention did not change. The time at which sustained attention was measured can explain this finding. Usually, vigilance is higher in the morning than in the afternoon. Possibly, slight changes, induced by melatonin, could be better detected when tests measuring vigilance are performed in the afternoon. Furthermore, the time necessary to perform the Bourdon-Vos test (10 minutes) could have been too short to detect slight changes in sustained attention. Another possibility is that the sustained attention was not impaired enough to be improved by melatonin treatment.

The dose of melatonin and the time of administration remain a matter of discussion. We administered 5 mg of melatonin, based on the favorable results of Jan and Donnell,[12] who treated successfully more than 100 mentally handicapped children with 2.5- to 10-mg melatonin. This dose is much higher than the 0.3 mg that Zhdanova et al[14] used in the treatment of 13 children with Angelman's syndrome. Lewy et al[31] showed that melatonin maximally advances circadian rhythms when administered 5 hours before melatonin onset. Five hours before melatonin onset should have meant that several children should have to take the melatonin at 4 PM. In a pilot study, we found that most children who received melatonin at that time became intolerably sleepy within 30 to 60 minutes after melatonin intake.

Mild generalized epilepsy, which developed in one child, could be induced by melatonin.[32] However, melatonin also has an anticonvulsant action, as shown by animal and human

studies.[12,33] After all, it is well known that better sleep results in improved seizure control.[12] Furthermore, the antioxidant activity of melatonin may also result in relief of seizures.[34]

Although melatonin and its metabolites are not mutagenic, and melatonin possesses remarkably low acute toxicity in animals and humans, it is difficult to exclude the toxic effects of long-term treatment.[35] Therefore, continuous use of melatonin reinforcing sleep disruption in young children requires very careful assessment. In particular, the potential reproductive effects are of primary importance in children.[36]

The improved behavior, mentioned by several parents during the follow-up, could have been induced by improved sleep. Probably, the improved sleep had diminished the manifestations of sleep loss (ie, irritability, crankiness, low-frustration tolerance, and short attention span).[3]

The question why 5 mg of melatonin is effective in children with sleep onset insomnia cannot be answered yet. We speculate that both hypnotic and chronobiotic effects play a role. The drowsiness, which occurs within 30 to 60 minutes after melatonin intake and which usually diminishes about 1 hour later, can be considered as the hypnotic effect.[37-39] This drowsiness may induce sleep. The advancement of the endogenous melatonin production can be considered as the chronobiotic action of melatonin.[34] The start of the endogenous melatonin secretion opens a sleep gate, which induces sleep.[30] Consequently, the advancement of the endogenous melatonin onset can induce advancement of sleep onset.

The advancement of the endogenous melatonin onset, induced by the melatonin treatment, does not mean that the sleep problem was cured. A sleep problem is only genuinely cured when the sleep remains normal after stopping the drug.

Chronic treatment-resistant insomnia is a great burden for both children and their families. Our study suggests that melatonin treatment might be of great help. Not only does sleep improve but possibly also daytime behavior.

As long as optimal dosage, toxicity, and long-term effects of melatonin have not been documented, well-performed trials to resolve the many unanswered questions are urgently needed. In anticipation of the results, treatment with melatonin might be considered in countries where melatonin is available over the counter. However, we recommend restricting melatonin to children with severe treatment-resistant chronic sleep onset insomnia and a delayed dim light melatonin onset. The lowest effective dose should be sought and treatment should be stopped at least once a year (eg, during holidays) to find out if the sleep problem has been cured in the meanwhile.

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