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Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia

Abstract: We conducted this study to assess long-term melatonin treatment course, effectiveness and safety in children with attention-deficit/hyperactivity disorder (ADHD) and chronic sleep onset insomnia (CSOI). This was conducted by means of a structured questionnaire for the parents. The subjects of this study consisted of participants who previously participated in a randomised clinical trial on melatonin efficacy. The response rate was 93% (94/101). The mean time to follow up was 3.7 yr. No serious adverse events or treatment related co-morbidities were reported. Sixty-five percent of the children still used melatonin daily and 12% occasionally. **Temporal discontinuation of treatment resulted in a delay of sleep onset in 92% of the children.** Nine percent of the children could discontinue melatonin completely because of improvement of sleep onset insomnia. Long-term melatonin treatment was judged to be effective against sleep onset problems in 88% of the cases. Improvement of behaviour and mood was reported in 71% and 61% respectively. We conclude that melatonin remains an effective therapy on the long term for the treatment of CSOI in children with ADHD and has no safety concerns regarding serious adverse events or treatment related co-morbidity. Discontinuation of melatonin treatment usually leads to a relapse of sleep onset insomnia and in resuming melatonin treatment, even after several years of treatment.

Michel Hoebert^{1,5}, Kristiaan B. van der Heijden², Ingeborg M. van Geijlswijk^{3,4} and Marcel G. Smits⁵

¹Department of Neurology, Elisabeth Hospital, Tilburg; ²Clinical Child and Adolescent Studies, Leiden University, Leiden; ³Faculty of Veterinary Medicine, Pharmacy Department, Utrecht University, Utrecht; ⁴Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht; ⁵Department of Neurology, Sleep-Wake Disorders and Chronobiology, Hospital de Gelderse Vallei, Ede, the Netherlands

Key words: ADHD, children, chronic sleep onset insomnia, long term follow-up, melatonin

Address reprint requests to Dr Marcel G. Smits, Hospital Gelderse Vallei, P.O. Box 9025, 6710 HN Ede, the Netherlands.
E-mail: smitsm@zgv.nl

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Introduction

Chronic sleep onset insomnia (CSOI) is frequently reported in children with attention-deficit/hyperactivity disorder (ADHD) with rates up to 28% in medication-free children with ADHD [1, 2]. In the general child population, insomnia is associated with daytime fatigue, impaired daytime functioning and impaired health status [3–5]. A recent study demonstrated that children with ADHD and CSOI showed a delayed sleep-wake rhythm with normal sleep maintenance as well as a delayed increase of endogenous melatonin in the evening [6]. Properly timed exogenous melatonin in the afternoon or evening advances endogenous melatonin secretion in the evening, facilitating sleep onset at an earlier time [7, 8]. Short-term melatonin treatment, i.e. several weeks, has proven to be safe and effective for the treatment of CSOI in children with ADHD [9–11]. The number of clinical trials on melatonin treatment in children with insomnia increases, and with that the evidence for its efficacy and safety in the short-term. However, there is limited information available on the long-term effectiveness and

safety of melatonin therapy. Most studies assessing effectiveness and safety of exogenous melatonin therapy in children included a short follow-up duration of several weeks [12]. Only few studies included a longer follow-up time, but the numbers of participants were small [13, 14].

Recently, one study assessed prospectively long-term effectiveness and safety of melatonin treatment in children with neurodevelopmental disabilities [15]. Mean follow-up duration was 3.8 yr. Effectiveness of long-term melatonin therapy was rated by the caregivers as highly positive. Adverse reactions were not found.

The results of this study, however, relate to a heterogeneous group of children with multiple neurodevelopmental disabilities and may not be applicable to the general child population or other clinical populations such as children with ADHD. Furthermore, several clinically relevant questions on melatonin treatment remained unanswered, such as the degree of relapse of sleep onset insomnia after stopping melatonin and the long-term effects of melatonin treatment on sleep improvements, behaviour and mood in children with ADHD.

To assess relapse rate of sleep onset insomnia after discontinuing melatonin treatment and to obtain more data about effectiveness and safety of long-term melatonin treatment in children with ADHD, we conducted a long-term follow-up study in children who previously participated in a randomised clinical trial (RCT) [9].

Method

Subjects and procedures

The parents of all 105 children who previously participated in a randomised, double blind, placebo-controlled trial on melatonin treatment [9] were accessed by telephone between September 2007 and February 2008, to ask for participation in the present follow-up study. The previous trial was conducted between November 2001 and June 2005 and inclusion criteria were: age 6–12 yr, rigorously diagnosed ADHD, a total IQ higher than 80 and chronic sleep onset insomnia. Children who were assigned to melatonin received a dose of 3 mg when body weight was < 40 kg and 6 mg when body weight was ≥ 40 kg. At the end of the trial period, all participants were offered melatonin treatment in the context of regular care by specialised physicians. Treatment effect, dosage and time of administration were discussed with the parents at regular control appointments with the prescribing physician. The prescribing physician encouraged to discontinue melatonin treatment every year for at least 1 wk during a holiday period to evaluate whether melatonin treatment was still necessary.

At inclusion of the RCT parents gave written consent to be questioned several years later about the long-term treatment effects. The study was approved by the Institutional Review Board and by the Medical Ethical Committee. After the parents had given verbal permission during the phone call for participation in the present follow-up study, they were requested to fill in and return a questionnaire. The questionnaire was sent to them, together with a detailed information letter and a return envelope. Parents who did not return the questionnaire were accessed by telephone for a second time and requested once again to return the questionnaire.

Measures

The questionnaire consisted of a combination of multiple choice, numeric, open ended and scaled questions, 19 in total. These questions addressed the following topics: does the child still use melatonin, what is the current dosage, what is the time of administration, what were the reasons for discontinuation melatonin, did the child temporarily discontinue melatonin, what were the effects of discontinuation of melatonin on sleep and behaviour, did the child experience adverse events, did the child experienced unusual co-morbidity during melatonin treatment and what were the effects of melatonin treatment on sleep onset problems, behaviour and mood.

A provisional version of the questionnaire was pilot tested by means of a short questionnaire in a sample of five individuals to assess the feasibility and clarity of the items and response categories. The evaluation results were

positive and no adjustments of the questionnaire were needed.

Data analysis

The chi-squared test was applied to analyse the difference between the group who did or did not temporarily discontinue treatment in the variable regarding complete discontinuation of melatonin treatment at follow up.

The Mann–Whitney *U*-test was applied to analyse the difference in pretreatment dim light melatonin onset (DLMO) between the children who discontinued treatment completely because of improvement of sleep onset insomnia and of the remainder of the group. The Mann–Whitney *U*-test was applied to analyse the difference in pretreatment DLMO between the children who used melatonin occasionally and the children who used melatonin daily. Effect sizes were calculated with the Pearson’s correlation coefficient. The Mann–Whitney *U*-test was applied to analyse the difference in age between the different groups mentioned above. Relationship between DLMO and age was analysed with the Pearson’s correlation coefficient.

Significance was set at $P \leq 0.05$ (two sided). Analyses were conducted using SPSS, 14.0 (SPSS, Inc, Chicago, IL, USA).

Results

One hundred and one parents were reached by telephone and all gave permission for participation in this study. Four children were lost to follow up. One hundred and one questionnaires were sent to the parents. The response rate in this study was 94/101 (93%). In total, data of 94/105 (89.5%) of the children participating previously in the melatonin trial [9] were included in this study. Seventy of 94 (74.5%) of the children were male. The mean (\pm S.E.M.) follow-up time of this study was 3.66 ± 0.12 yr. Mean age (\pm S.E.M.) at start of melatonin treatment was 8.72 ± 0.21 yr. Mean age (\pm S.E.M.) at follow up was 12.39 ± 0.25 yr.

Sixty-one (64.9%) children still used melatonin daily at the time of follow-up. Eleven (11.7%) children used melatonin occasionally. In most cases these latter children only used melatonin when they could not sleep. The frequency of melatonin usage in this group ranged from two to three times a week to a few times a year. **Twenty-two (23.4%) children discontinued melatonin treatment completely.** The current dose of melatonin in the group who still used melatonin ranged from a half to ten milligrams (mean \pm S.E.M.: 4.23 ± 0.27). Time of administration of melatonin ranged from 18:30 to 23:00 (mean 19:53). Eighty-two percent of the children took melatonin at a fixed time on weekdays. In the weekend 67% of the children took melatonin at a later time than on weekdays. Fig. 1 shows the parents’ opinion of melatonin treatment effect on sleep onset insomnia, behaviour and mood.

Twenty-two (23.4%) children discontinued melatonin treatment completely. The duration of using melatonin ranged from one to 57 months (mean \pm S.E.M.: 18.28 ± 3.0). The reasons for discontinuation and the

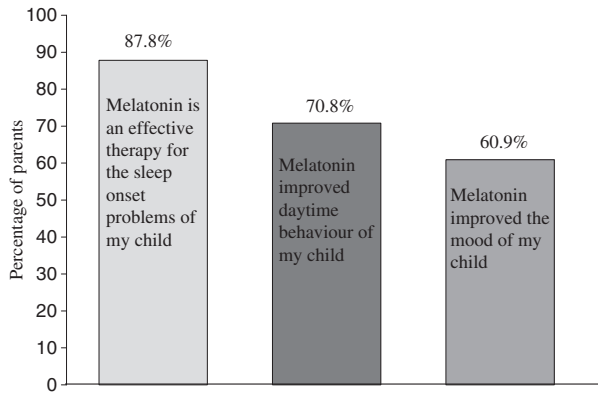


Fig. 1. Parents' opinion of melatonin treatment effect on sleep onset insomnia, behaviour and mood.

duration of treatment are presented in Fig. 2. The last applied dose of melatonin in the group who discontinued melatonin treatment ranged from three to ten milligrams (mean \pm S.E.M.: 5.73 ± 0.89).

Eight children discontinued melatonin treatment completely because of a total improvement of sleep onset insomnia. Three children discontinued the treatment because of adverse events. One child experienced profuse perspiration, especially during waking up, one child experienced persistent dizziness, visual disturbances, headache and daytime laziness and one child experienced headache, abdominal pain, nausea and excessive morning sedation. In

all three children the adverse events spontaneously resolved after discontinuation of melatonin.

In four children melatonin treatment was discontinued on the initiative of the treating physician. In two of these children the physician discontinued treatment because of concerns regarding the effects of long term treatment on pubertal development. In the other two children, the reason for discontinuing treatment by the physician was not reported.

The DLMO was assessed at the baseline phase of the randomised, double blind, placebo-controlled trial on melatonin efficacy [9]. The 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 [16]. We analysed pretreatment DLMO in the different groups of children in order to determine whether there is an association between pretreatment DLMO and successful discontinuation of treatment or decrease of melatonin intake.

The mean (\pm S.E.M.) pretreatment DLMO of the eight children who discontinued treatment completely because of improvement of sleep onset insomnia was $20:21 \pm 0.25$ hr, while this was $20:41 \pm 0.06$ hr in the remaining subjects ($P = 0.413$, effect size = -0.09). The mean (\pm S.E.M.) pretreatment DLMO of the eleven children who used melatonin occasionally was $20:11 \pm 0.15$ hr against $20:48 \pm 0.07$ hr in the 61 children who used melatonin daily ($P = 0.037$, ES = -0.26). Correction for age was not applied because of an absence of between-group differences in age.

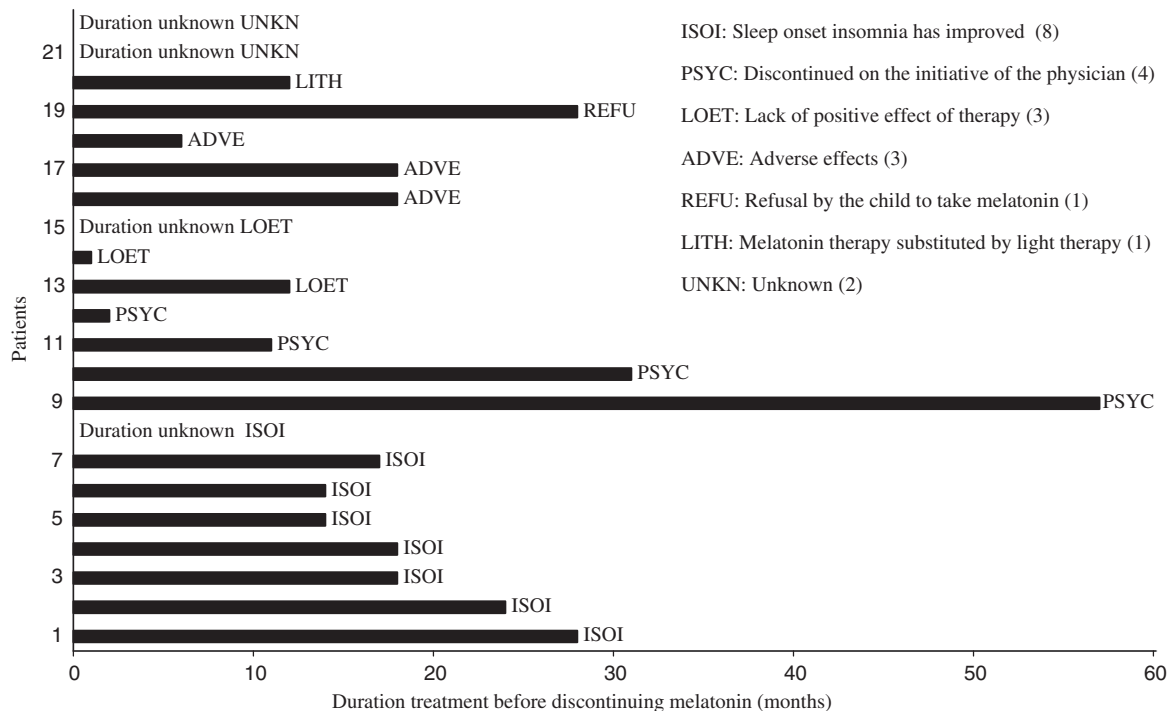


Fig. 2. Reasons for discontinuing melatonin treatment. The duration of treatment before discontinuing melatonin in months plotted out against each individual child who discontinued melatonin treatment completely. The reasons for discontinuing treatment and the number of patients (between brackets) are in the right corner.

During the entire treatment period, 67 (71.3%) children temporarily discontinued melatonin treatment, mostly during a holiday period, while 20 (21.3%) children never discontinued melatonin treatment (6.4% did not respond to this item). Of the children who temporarily discontinued melatonin, 14.9% did not use melatonin at follow-up, while this was 33.3% in children who did not temporarily discontinue melatonin ($\chi^2 = 3.48$; $P = 0.06$). The effect of temporary treatment discontinuation on sleep and behaviour is presented in Table 1.

Nineteen (20.2%) children experienced adverse events which they or the parents attributed to melatonin treatment. Adverse events are presented in Table 2. The majority of the parents (63.2%) reported multiple adverse events, seven parents (36.8%) reported one adverse event, four parents (21.1%) reported two adverse events, four parents (21.1%) reported three adverse events and four parents (21.1%) reported four adverse events.

In ten (52.6%) children the adverse events were self limiting. In six (31.6%) children the adverse events persisted, which was the reason to discontinue treatment in three out of these six children. Persistent adverse events were sleep maintenance insomnia, excessive morning sedation, decreased mood and headache, profuse perspiration and daytime laziness. In three children (15.8%) it was not mentioned in the questionnaire whether the adverse events were self limiting or not.

Seven (7.4%) parents reported unusual co-morbidity in their children. Co-morbidity they reported were: pertussis, pneumonia, adverse reaction after general anaesthesia, coeliac disease and food allergy, Osgood-Schlatter disease, viral eye infection and visual disturbances (the ophthalmologist did not found a cause for the visual disturbances). None of the children had epilepsy before they started with melatonin treatment. During the follow-up period no new cases of epilepsy developed.

Discussion

This is the first study to assess long-term treatment course, effectiveness and safety of melatonin in children with

Table 1. Effect of discontinuing melatonin treatment on sleep and behaviour

Effect	No. of children (%)
No change of sleeping pattern	1 (1.5)
Delay of sleep onset time	60 (92.3)
Delay of wake up time	20 (30.8)
Changing daytime behaviour	19 (29.2)

ADHD and insomnia and to evaluate the effect of discontinuation of melatonin on sleep and behaviour in these children. Nearly all children who temporarily discontinued melatonin experienced a delay in sleep onset time. The majority of these children (85.5%) were still using melatonin at follow-up, which was on average almost 4 yr after treatment commencement. Temporary discontinuation did not increase the chance of permanent discontinuation significantly. **These results suggest that phase advancing effects of melatonin on the circadian pacemaker rhythm are not persistent and that phase delay usually reoccurs after treatment is discontinued.** Hence, we conclude that melatonin normally ameliorates CSOI in children with ADHD only for as long as the treatment is continued but does not cure it completely. The delayed sleep-wake rhythm in these children could be partly genetically determined. Recently it was found that a polymorphism of the Per three clock gene, one of the genes involved in the mechanisms of the biological clock, is associated with adult ADHD [17]. This polymorphism has been implicated in eveningness preference in humans and delayed sleep timing.

In elementary school children with chronic sleep insomnia, pretreatment DLMO predicts effectiveness of melatonin treatment, as the later the DLMO, the more sleep onset advances [18]. In this study mean pretreatment DLMO of children who used melatonin occasionally was significantly earlier than the DLMO of the children who used melatonin daily. This suggests that pretreatment DLMO also predicts duration of melatonin treatment. However, mean pretreatment DLMO did not differ between children who discontinued treatment successfully and the rest of the children. Compared with the children who used melatonin daily, it is possible that the insomnia of the group of children who used melatonin occasionally consisted of a mixture of other types of insomnia (e.g. idiopathic insomnia, insomnia not occurring every day) involving an earlier DLMO and, therefore, using melatonin occasionally as a hypnotic drug instead of a chronobiotic. The children who used melatonin daily had more of the characteristics of a delayed sleep-wake rhythm considering the DLMO occurring at a later time.

Obtaining pretreatment DLMO has several therapeutic advantages. First, a delayed DLMO is diagnostically indicative of the presence of a circadian rhythm disorder and might therefore provide insight into the underlying pathology of the sleep problem. A relatively delayed value of DLMO indicates a delayed biological rhythm and therefore warrants chronobiotic treatment strategy. A relatively normal value of DLMO suggests that other

Dizziness, N (%)	4 (4.3)	Visual disturbances, N (%)	2 (2.1)
Bedwetting, N (%)	3 (3.2)	Excessive morning sedation, N (%)	2 (2.1)
Sleep maintenance insomnia, N (%)	3 (3.2)	Constipation, N (%)	1 (1.1)
Headache, N (%)	2 (2.1)	Profuse perspiration, N (%)	1 (1.1)
Nausea, N (%)	2 (2.1)	Decreased mood, N (%)	1 (1.1)
Skin pigment changes, N (%)	2 (2.1)	Daytime laziness, N (%)	1 (1.1)
Nightmares, N (%)	2 (2.1)	Change in behaviour, N (%)	1 (1.1)

Table 2. Adverse events reported during melatonin treatment

underlying causes may be present such as psychiatric problems (e.g. depression and anxiety). This requires a treatment approach focussed on reduction of these underlying causes. Secondly, pretreatment DLMO predicts treatment success. Van der Heijden et al. showed that the later the DLMO the more sleep onset and DLMO advances after treatment [18]. In practice this means that in a child with sleep onset insomnia and moderately delayed DLMO, who does not or only mildly respond to melatonin treatment, melatonin can be stopped soon. However, in a child with sleep onset insomnia and severely delayed DLMO, who does not respond well to melatonin, much more efforts have to be taken to achieve treatment success, i.e. changing dose or time of administration. Thirdly, starting melatonin treatment without measurement of DLMO might lead to reduced treatment effects or even to phase shifts in sleep-wake rhythm that are in the opposite direction of the desired effect, when melatonin is administered after DLMO. Several patients with such history were referred to our Dutch national referral centre for sleep-wake disturbances and chronobiology. Repeated measurements of DLMO in these patients showed that it can last several months before a stable melatonin rhythm is reached which is likely to be representative of the melatonin rhythm before the start of melatonin treatment. Therefore, the time period needed before representative DLMO values can be obtained results into a considerable delay.

For the reasons mentioned above we recommend to measure DLMO before treating patients with melatonin or melatonin analogues. Labs which can measure DLMO for clinical purposes are listed at: <http://www.DLMO.org>.

This study showed that long-term use of exogenous melatonin in children continued to be an effective therapy for sleep onset insomnia. This corresponds with the results of a small open label study of melatonin treatment in children with ADHD reporting that the effect of melatonin persisted for at least 3 months [11]. We also found that long-term melatonin treatment seemed to improve behaviour and mood. In the previous RCT [9] 4 wk of melatonin treatment did not improve these insomnia associated aspects. Because of the uncontrolled design of our study, it remains unknown to what extent placebo effects are responsible for the long-term treatment effects on behaviour and mood.

Approximately one fifth of the children experienced adverse events. Most frequently reported adverse events were dizziness, sleep maintenance insomnia and bedwetting. In three out of 94 children, treatment was discontinued because of adverse events, which resolved after discontinuation of medication in all children. The rate of adverse events was higher than in the long-term follow-up study of Carr et al. [15]. This could be because of the fact that we only asked to report adverse events, without asking if the parents thought these were related to melatonin or to another co-treatment. Consequently, adverse events caused by methylphenidate could have been reported and attributed to melatonin. At the start of the follow-up period, none of the children used stimulant medication but given that all children were diagnosed with ADHD, it is to be expected that the greater part of the children have started with stimulant medication during the follow-up period.

Another explanation for the higher rate of adverse events in our study may be that our sample consisted of children with ADHD without intellectual disabilities, in contrast with the study group of Carr et al. [15] which was composed of children with neurodevelopmental disabilities. It is possible that these children experienced and reported fewer adverse events than children without neurodevelopmental disabilities, leading to a lower adverse event rate. Most short term trials of melatonin treatment in children with intellectual disability have reported no adverse events [19] in contrast to comparable studies in children with ADHD [9–11] as well as in children without ADHD or neurodevelopmental disabilities [20, 21]. Because of the lack of a placebo group in our study, other causes of the reported adverse effects cannot be ruled out. However, because of the long duration of the evaluation period, the inclusion of placebo treatment would have been unethical. This way of evaluation is comparable to the worldwide postmarketing surveillance programs to evaluate adverse events of medication after registration.

Melatonin dependence or rebound insomnia was not reported after discontinuing melatonin. We usually advise all patients (children and adults) to discontinue melatonin treatment each year during at least 1 wk (preferably during the summer). So far, nobody did report melatonin dependence, rebound insomnia or withdrawal symptoms. To our knowledge no studies have been published that investigated these topics systematically in children or adults. A recent review of the melatonin receptor agonist ramelteon stated that this drug is not associated with withdrawal symptoms, rebound insomnia or abuse potential in adults [22]. Given that exogenous melatonin has a comparable mode of action to that of ramelteon, to some extent, these conclusions could be extrapolated with caution to exogenous melatonin.

The dose of melatonin used at follow-up ranged from a half to ten milligrams and did not differ from doses used in other studies. A recent review of melatonin treatment of sleep disorders in children with intellectual disabilities concluded that a wide range of doses of melatonin are used in children, but most of the trials with a positive result used a dose of 2.5 mg and above [19]. Another review of melatonin treatment in children with neurodevelopmental disabilities showed that the dose of melatonin used in these children ranged from 2 to 10 mg. None of the doses was associated with significant adverse effects [23]. Studies showed that there is much variability in the response to melatonin, while a dose/weight relationship has not yet been described. We are currently performing a dose finding trial in children to establish the optimal dose. In our experience, effective melatonin doses usually can be less than 6 mg in children aged 6–12 yr with chronic sleep onset insomnia and delayed DLMO.

In most studies in children, melatonin was administered close to the desired bed-time [19, 24]. The time of melatonin administration at follow-up in our study had a great range of dispersion, ranging from 18:30 to 23:00. The explanation for this is that at the start of the placebo controlled trial melatonin was administered at 19:00. After the trial period some children wanted to delay the acute sleepiness attributed to the direct soporific effect of melatonin. When lowering the dose was either not effective to eliminate this

effect or when at a lower dose the positive effect of melatonin on sleep-wake rhythm was reduced, the solution was found in delaying administration towards bed time.

In this study, 7.4% of the children developed various co-morbid conditions during melatonin treatment. Three children experienced an infectious disease (pertussis, pneumonia and a viral eye infection). Theoretically, it is possible that these children were more prone to infections because of exogenous melatonin use. However, exogenous melatonin has an immunostimulatory effect rather than an immunosuppressing effect [25]. One child developed a food allergy and one child was diagnosed with coeliac disease. Melatonin appears to have an immunomodulatory effect in allergic diseases and may play a role in the regulation of asthma [26]. The role of melatonin in food allergy and coeliac disease is not known, but considering the immunomodulatory effect of melatonin, a contribution of exogenous melatonin in the pathogenesis of food allergy or coeliac disease can not be completely excluded. One child experienced an adverse reaction after general anaesthesia, but melatonin administration is reportedly associated with a tendency towards faster recovery after general anaesthesia [27]. The arguments mentioned above, make it unlikely that this co-morbidity is directly related to melatonin treatment.

During the follow-up period no new cases of epilepsy developed. This is consistent with the literature showing that melatonin has no clear pro-convulsive effect [19]. None of the children in our study had epilepsy, so the chances of melatonin triggering seizures were small whatsoever. Only one small uncontrolled study reported a pro-convulsive effect of exogenous melatonin in children with neurodevelopmental abnormalities [28].

Some evidence suggest that exogenous melatonin alters semen quality in adult men [29] and influences the levels of prolactin, luteinising hormone, progesterone and oestradiol [30, 31], but other research found no influence of exogenous melatonin on the secretion of pituitary-gonadal hormone secretion in men [32]. The onset of puberty is associated with a significant reduction in nocturnal melatonin levels [33] and melatonin might play an inhibitory role on puberty [34]. These findings raise some concerns that exogenous melatonin in children might influence the human reproduction system and the onset of puberty [35]. However, there is no clinical or research evidence after so many years that exogenous melatonin significantly influence the onset of human puberty. The effects of long-term use of melatonin on pubertal development and fertility could not be properly assessed by our study design. Ideally, this should be performed prospectively by frequently assessing Tanner stages in adolescence or fertility in adulthood preferably with matched control groups. However, given the great interindividual variability in pubertal development, expected small negative effect sizes on fertility, and the presence of various confounding factors influencing fertility such studies would be complicated and required large sample sizes. The only study thus far which assessed effectiveness and safety of long-term melatonin treatment in children gave comparable results to our study [15]. This prospective follow-up study evaluated a smaller and more heterogeneous group of 44 children with multiple neurodevelopmental disabilities

who participated in a placebo-controlled double blind melatonin trial. The authors found that the onset of signs of puberty was age appropriate suggesting a normal pubertal development.

The fact that the parents who reported adverse events were not carefully interviewed is a limitation of our study. In one item in the questionnaire we did ask, in case of reported adverse events, how long after the start of the melatonin therapy the adverse event(s) occurred. A lot of parents did not answer this question or the answers were variable (the adverse events occurred days to months after initiation of melatonin therapy).

Associating adverse events with a specific drug or treatment in a long-term follow-up trial is a limitation in general because of the lack of a long-term placebo arm and because of the occurrence of possible non controlled changes in the environment of the study participants. An interview with the parents could have given more information about the relation between reported adverse events and the melatonin treatment. However, it was difficult to find a satisfactory trade-off between a long follow-up duration on the one hand and a detailed but laborious and invasive study methodology using frequent interviews with the parents of the participants on the other hand.

Other limitations of our study are the fact that we did not ask systematically for co-medication, the lack of measures to assess long-term effects of melatonin treatment on pubertal development and fertility, the retrospective design and the lack of control treatment.

Strengths of this study are the relatively large sample size of 94 patients, the comprehensive questionnaire, and the high response rate of 93%. The subjects of this study are children with rigorously diagnosed ADHD including all subtypes, which makes the results of this study applicable to the population of patients with ADHD and sleep onset insomnia. Furthermore, the exclusion of children with mental retardation in the previous RCT increases generalisability to the normal child population. However, caution is warranted as it remains unknown whether the particular long-term effects in this study are specific to the population of children with ADHD because of, for example other treatments, underlying morbidity or genetic factors specific for this group.

To conclude, long-term use of exogenous melatonin did not show safety concerns in children regarding serious adverse events and treatment related co-morbidity. Melatonin remains an effective therapy on the long-term for the treatment of sleep onset insomnia in children with ADHD, however, it does not provide a permanent cure. **Even after several years of treatment, discontinuation of melatonin treatment often leads to a relapse of sleep onset insomnia and to resuming melatonin treatment.**

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