Melatonin treatment and light therapy for chronic sleep onset insomnia in children

Effects on sleep, cognition, health, and psychosocial functioning

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CHAPTER 2

Termination of short term melatonin treatment in children with chronic sleep onset insomnia

Effects on sleep, health, behaviour problems, and parenting stress

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Van Maanen, A., Meijer, A. M., Smits, M. G., & Oort, F. J. (2011). Termination of short term melatonin treatment in children with delayed Dim Light Melatonin Onset: Effects on sleep, health, behavior problems and parenting stress.
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ABSTRACT

Objective: *To investigate the effects of termination of short term melatonin treatment on sleep, health, behaviour and parenting stress in children with chronic sleep onset insomnia.*

Methods: *41 Children (24 boys, 17 girls; mean age = 9.43 years) entered melatonin treatment for three weeks and then discontinued treatment by first taking a half dose for one week and then stopping completely for another week. Sleep was measured with sleep diaries filled in by parents and with actometers worn by children. Analyses were conducted with linear mixed models.*

Results: *Sleep latency was longer during stop week compared to treatment. Sleep start was later and actual sleep time was shorter during half dose and stop week compared to treatment. Sleep efficiency deteriorated in the stop week. Dim Light Melatonin Onset was earlier after treatment, but this effect disappeared after the stop week. In addition to the effects on sleep, results from questionnaires completed by parents showed that there were also positive effects of melatonin treatment on children's health and behaviour problems and parenting stress. While health deteriorated after treatment discontinuation, the effects on behaviour problems and parenting stress remained. Behaviour problems at baseline did not influence the effect of melatonin treatment.*

Conclusions: *This study showed that complete termination of treatment after four weeks of melatonin use was too early. However, clinicians may advise a lower dose after a successful treatment trial of several weeks.*

INTRODUCTION

Sleep onset problems are common among children. Different studies report prevalence rates varying from 11[1] to 30[2] or even 40%[3] of school age children who have problems with falling asleep. Considering the negative consequences of sleep problems on health, interpersonal relations, psychological functioning, daily activities,[4,5] and school functioning,[6,7] it is important to treat these problems.

The pineal hormone melatonin plays a central role in the synchronization of circadian rhythms, especially the sleep-wake rhythm. Its secretion is inhibited during the day, but increases at night.[8] In some children endogenous melatonin secretion is delayed, which makes that they cannot fall asleep at an appropriate time. This delay in melatonin secretion might be associated with a Per3 polymorphism in rare cases.[9] Exogenous melatonin, if well timed and administered in the right dose, can phase-shift the melatonin and sleep-wake rhythm.[10]

Although many studies showed that melatonin treatment has direct positive effects on sleep onset and health,[11-13] optimal treatment duration has not yet been established and is mostly patient dependent. Consequently, melatonin is often used for an indefinite time and patients are advised to stop every now and then to see whether sleep problems return.[14,15] Although several studies presented results after a relatively short treatment time,[11-13] information concerning discontinuation of treatment is missing. Because more knowledge about effects of treatment discontinuation in different phases of treatment (short, medium, long) can help to find optimal times for treatment termination, we explored the effects of short term treatment. An additional reason for examining short term treatment effects is that there is a (theoretical) risk that delayed puberty onset is related to long melatonin use.[16]

There is only one study[17] that examined the effects of termination of short term (3 weeks) melatonin treatment on sleep, health and behavioural variables. In this pilot study, the positive effects of melatonin disappeared almost completely after abrupt treatment discontinuation. As the abrupt discontinuation of melatonin might have diminished the effects of melatonin on sleep, in the present study we examined the effects of half-dose treatment and thereafter complete discontinuation of melatonin. An additional advantage of half-dose treatment is that we can also investigate whether a lower dose is still effective. To our knowledge, this study is the first study investigating effects of half dose and discontinuation of short term melatonin treatment in children.

In addition to the chronobiotic (phase-advance) and hypnotic (sleep promoting) effect, we also examined effects of termination of melatonin on health, behaviour problems, and parenting stress. Sleep, health, behaviour problems, and parenting stress appear strongly related.[4,5,18-20] Therefore, we hypothesised that melatonin treatment not only would have positive effects on sleep, but also on these other variables. We expected the positive effects on health, behaviour problems, and parenting stress to remain after melatonin discontinuation only in case the positive effects on sleep remained. The question whether behaviour problems influence the effects of melatonin treatment and melatonin termination was also examined in the present study.

METHODS

Participants

The study was conducted in the Centre for Sleep-Wake Disorders and Chronobiology in a hospital in the Netherlands. Children were referred to the hospital by their general practitioners because of their sleep onset problems. Inclusion criteria for participation were: (1) age between 5 and 12 years old, (2) the child has chronic sleep onset problems defined as (a) complaints of sleep-onset problems expressed by parents and/or child, (b) occurrence on at least 4 days/week for longer than 1 year, (c) average sleep onset later than 20:15 hours for children at age 5 years and for older children 15 minutes later per year, and (d) average sleep latency exceeding 30 minutes, (3) Dim Light Melatonin Onset (DLMO) later than 20:00 hours, (4) the child attends a regular school (IQ is in the normal range) and (5) parents of the child have sufficient command of the Dutch language in order to understand the treatment and complete the questionnaires. Children were not eligible for participation if (1) the child had a diagnosis of another sleep disorder (e.g., restless legs syndrome, narcolepsy, obstructive sleep apnoea syndrome), and/or (2) the sleep onset problems were caused by physical problems (e.g., pain).

In total, 43 children of the 98 children younger than 18 years that were referred for treatment met the inclusion criteria. Two families decided not to participate in the study, leaving a final sample of 41 children and their parents. Of these 41 children, 24 were boys (58.54%) and 17 were girls (41.46%). Mean age was 9.43 years (SD = 2.05, range 5.42 - 12.67). Eight children had a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), five children were diagnosed with an autism spectrum disorder and one child with both. Most parents were married (87.8 %) and 43.9 % completed higher education levels.

Procedure

The study was approved by the ethical committee of our research institute. Parents gave active informed consent for publication of the results. Inclusion of participants took place from September to December 2009. Before their first appointment in the hospital, parents completed a sleep diary and some questionnaires regarding the sleep problem of their child. Dim Light Melatonin Onset, the clock time at which the endogenous melatonin secretion reaches a certain threshold, was measured in saliva. Parents were asked to instruct their children to chew on cotton plugs according to a predetermined schedule for one evening.[11,13]

In order to make sure all participants had similar knowledge about sleep hygiene practices, this topic was discussed during the first appointment in the hospital and written instructions for sleep hygiene were provided. Treatment started on the first Sunday after the appointment in the hospital. All children were instructed to start with a dose of 1 milligram. If parents did not see any effect of melatonin use after four days, they were allowed to increase the dose to 2 milligrams. If this still had no effect, the dose could be further increased to 3 milligrams up to maximally 5 milligrams. After three weeks of melatonin treatment parents filled in the questionnaires and children chewed on the cotton plugs. Then treatment was discontinued by first taking a half dose for one week (hereafter called "half dose week") and then stopping completely for another week (hereafter called "stop week"). After this stop week the same measures were taken. Parents filled in sleep diaries and children wore actometers during this whole period of five weeks. Families received reminders through text messages or e-mails on days that questionnaires had to be filled in, children had to chew on cotton plugs, or melatonin dose had to be halved. In addition, all families were contacted by telephone twice during this study to discuss their experiences: once in the first week of treatment and once after the end of the stop week. Children were allowed to recommence with melatonin after the last day of the stop week.

The study (Fig. 1) consisted of three measurements: baseline (in the week before the start of treatment; T0), directly after three weeks treatment (T1), and at the end of the stop week (T2). At these measurement occasions DLMO was determined in saliva and questionnaires were filled in. Behaviour problems were measured twice (at baseline and at the end of the stop week), because of the length of the questionnaire. As we were primarily interested in the effects of half dose and termination of treatment on sleep, we used treatment data from the first three weeks as baseline for the sleep data.

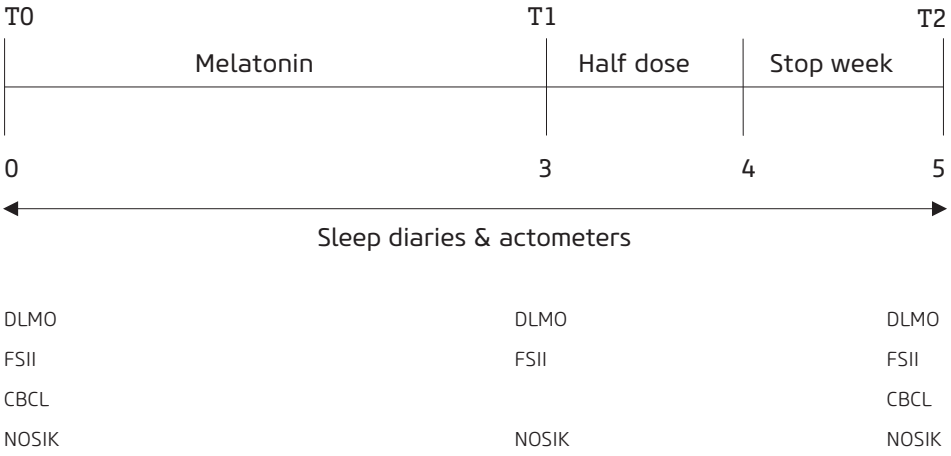

Figure 1. Study design

DLMO = Dim Light Melatonin Onset; FSII = Functional Status II; CBCL = Child Behavior Checklist; NOSIK = Nijmegen Parental Stress Index short version.

Measures

Sleep

Sleeping behaviour was measured with actometers and with sleep diaries filled in by parents. Parents filled in sleep diaries daily via internet. The sleep diary consisted of questions concerning bed time, lights off time, sleep onset time and whether the child woke up during the night. Sleep latency (time children spent in bed before falling asleep) and sleep start were used as sleep parameters in the analyses.

Actometers, miniaturised computerised wristwatch-like devices to monitor and collect data generated by movements,[21] can distinguish between sleep-wake states by measuring movement. They were used to obtain objective information about sleep latency, sleep start, actual sleep time (time children actually slept during the night) and sleep efficiency (actual sleep time/time in bed).

Dim Light Melatonin Onset

Dim Light Melatonin Onset, considered to best represent adjustment of the biological clock[22] was measured in saliva, using Buhlmann RIA kits. Children chewed on cotton plugs hourly from 19:00 to 23:00 hours in the evening at dim light.[11,13] Children were not allowed to use melatonin the evenings at which DLMO was measured.

Health

Health status of children was measured with the first part of the Functional Status II (FSII).[23,24] This first part has 14 items concerning activities and behaviours in the past two weeks. Parents had to indicate how often these behaviours or activities occurred on a three-point scale varying from (0) "never or rarely" to (1) "some of the time" and (2) "almost always". A higher score indicates a better functional status and a better health. Cronbach's alpha varied between 0.57 and 0.82 for mothers and fathers at different measurement occasions.

Behaviour problems

Behaviour problems in children were measured with the Child Behavior Checklist (CBCL).[25,26] The CBCL is a comprehensive (112 items) questionnaire containing broad band scales and narrow band scales. In this study only the broad band scales measuring internalising and externalising behaviour problems were used. The response scale ranged from (0) "not true" to (2) "very true or often true", with a higher score indicating more behaviour problems. Reliabilities took on values between .85 and .90 and .91 and .92 for internalising and externalising problems respectively. For total problems the reliability varied from .95 to .96.

Parenting stress

Parenting stress was measured with the Nijmegen Parental Stress Index short version (NOSIK).[27] The NOSIK is a questionnaire with 17 items that measures to what extent parents experience stress in parenting their child. Parents answered the items on a 4-point scale, ranging from (1) "strongly disagree" to (4) "strongly agree". A higher score indicated more parenting stress. Reliability varied from .93 to .95.

Statistical analysis

Data were analysed using linear mixed models in SPSS,[28] treating the repeated observations as nested within children. In this way all available data were used to answer the research questions, including data from children with missing observations. For each outcome variable, it was first determined which longitudinal structure described the variances and covariances best.[29] For all sleep variables and for parenting stress a first-order autoregressive covariance structure was chosen. For health and behaviour problems diagonal covariance structures were used.[30] In the second step, predictors were added to the model and fit of the models was compared. If addition of predictors significantly improved the fit, the regression coefficients were interpreted.

For the main research question (about the effects of half dose treatment and termination of treatment on sleep, health, behaviour problems and parenting stress), outcome variables were DLMO, sum scores for the different questionnaires measured at T0 through T2, and sleep variables measured during the different phases of the treatment (treatment weeks, half dose week, stop week). Differences between treatment phases were tested by including binary indicator variables for phases in treatment as explanatory variables in the regression analysis. Weekend was included separately to account for different sleeping behaviour in weekends. Changes in DLMO and questionnaire data were tested by including binary indicators for measurement occasions as explanatory variables.

For the second research question (whether behaviour problems influenced the effect of melatonin treatment), the main effect of CBCL score at baseline and the interaction effects of CBCL with treatment phases were included in the models with the sleep variables mentioned above. If the fit of the model significantly improved after adding these effects, we examined which of the main and interaction effects were significant. If the global test of the interaction effects was significant, we examined the effects of CBCL at the different treatment phases separately.

RESULTS

Sleep outcomes and Dim Light Melatonin Onset

Sleep latency and sleep start means obtained from diary data are reported in Table 1. The results showed that sleep latency was significantly longer during stop week compared to treatment. The difference between treatment and half dose treatment was not significant. The results for sleep start were somewhat different. During half dose and stop week, children fell asleep later than during treatment (Table 2).

Results for the actometer data were in accordance with the results of the sleep diary. Sleep latency was longer in the stop week compared to treatment and the difference between treatment and half dose week was not significant. Sleep start was later during half dose and stop week compared to treatment. Actual sleep time was shorter during half dose and stop week than during treatment. For sleep efficiency, the difference between treatment and half dose was not significant. Only during stop week sleep efficiency was lower than during treatment (Table 2). Compared to baseline, DLMO was significantly earlier after three weeks treatment but this effect disappeared at the end of the stop week.

Health, behaviour problems, and parenting stress

Health scores significantly improved after treatment. This effect disappeared after the stop week. Internalising, externalising and total behaviour problems all had significantly decreased after the stop week, compared to baseline. Parenting stress decreased after treatment and was still decreased after the stop week.

Table 1 Means for sleep, DLMO, health, behaviour problems and parenting at the different measurement occasions and phases of treatment

HYPNOTIC SLEEP VARIABLES	TREATMENT M (SD)	HALF DOSE M (SD)	STOP WEEK M (SD)
Sleep latency (sleep diary; in minutes)	37.27 (28.47)	38.77 (34.36)	69.39 (46.77)
Sleep start (sleep diary; clock time)	21:00 (0:59)	21:11 (1:14)	21:43 (1:06)
Sleep latency (actometer; in minutes)	28.37 (26.90)	28.42 (27.28)	63.63 (43.63)
Sleep start (actometer; clock time)	21:07 (1:07)	21:29 (1:15)	22:08 (1:16)
Actual sleep time (actometer; in hours)	8.60 (1.05)	8.48 (1.02)	8.13 (1.03)
Sleep efficiency (actometer)	75.72 (7.31)	75.57 (7.19)	72.34 (7.13)
OTHER VARIABLES	**T0 (BASELINE) M (SD)**	**T1 (END OF TREATMENT) M (SD)**	**T2 (END OF STOP WEEK) M (SD)**
DLMO (clock time)	20:58 (0:50)	19:31 (0:52)	20:55 (1:09)
Health	20.88 (3.44)	22.65 (4.07)	20.92 (4.41)
Internalising behaviour problems	10.35 (8.26)		6.52 (6.54)
Externalising behaviour problems	10.61 (8.44)		7.68 (7.30)
Total behaviour problems	40.28 (23.37)		28.91 (21.09)
Parenting stress	32.32 (12.20)	29.84 (10.93)	29.70 (10.53)

DEPENDENT VARIABLE	FIXED EFFECTS	ß	S.E.	P
Sleep diary				
Sleep Latency	Half dose week vs. treatment weeks	2.893	2.759	.295
	Stop week vs. treatment weeks	32.742	3.001	< .001
	Weekend vs. week days (control variable)	-1.585	1.914	.408
Sleep Start	Half dose week vs. treatment weeks	11.058	3.525	.002
	Stop week vs. treatment weeks	49.691	3.808	< .001
	Weekend vs. week days (control variable)	26.533	2.651	< .001
Actometer				
Sleep Latency	Half dose week vs. treatment weeks	.401	2.384	.867
	Stop week vs. treatment weeks	36.625	2.642	< .001
	Weekend vs. week days (control variable)	.263	2.031	.897
Sleep Start	Half dose week vs. treatment weeks	25.877	4.186	< .001
	Stop week vs. treatment weeks	66.966	4.644	< .001
	Weekend vs. week days (control variable)	28.542	3.585	< .001
Actual Sleep Time	Half dose week vs. treatment weeks	-8.475	4.184	.044
	Stop week vs. treatment weeks	-28.242	4.639	< .001
	Weekend vs. week days (control variable)	8.557	3.819	.025
Sleep Efficiency	Half dose week vs. treatment weeks	-.221	.488	.652
	Stop week vs. treatment weeks	-3.736	.541	< .001
	Weekend vs. week days (control variable)	-1.383	.414	.001
DLMO	T1 (end of treatment weeks vs. baseline)	-87.901	11.632	< .001
	T2 (end of stop week vs. baseline)	-5.237	10.880	.633
Health	T1(end of treatment weeks vs. baseline)	1.818	.578	.002
	T2 (end of stop week vs. baseline)	-.065	.610	.915
Internalising behaviour problems	T2 (end of stop week vs. baseline)	-3.661	.662	< .001
Externalising behaviour problems	T2 (end of stop week vs. baseline)	-2.891	.646	< .001
Total behaviour problems	T2 (end of stop week vs. baseline)	-11.178	1.908	< .001
Parenting Stress	T1(end of treatment weeks vs. baseline)	-3.081	.833	< .001
	T2(end of stop week vs. baseline)	-3.381	1.040	.001

<< Table 2. Effects of treatment phases and measurement occasions on sleep, DLMO, health, behaviour problems and parenting stress in children with chronic sleep onset insomnia

Effect of behaviour problems on melatonin treatment

Only for the model with sleep latency measured with sleep diaries a significant effect was found. The effect of behaviour problems on sleep latency was negative (β = -.511, p = .030). This indicates that children with more behaviour problems have a shorter sleep latency in general. The interaction effect of behaviour problems with treatment phases was not significant (p = .083). Apparently, behaviour problems at baseline did not influence the effect of melatonin treatment on sleep.

DISCUSSION

The results showed that the positive effects of melatonin on sleep disappeared when treatment was completely discontinued. Sleep start and actual sleep time already deteriorated when children took a half dose. This can be explained by later bedtimes in the half dose week.

Melatonin treatment did not only improve sleep, but it also improved health and decreased behaviour problems and parenting stress. The positive effect of melatonin on health was also found in a previous study.[13] Although we are unaware of studies that found positive effects of melatonin treatment on behaviour problems and parenting stress, our findings support earlier research that found relations between sleep problems in children and behaviour problems and parenting stress.[5,18-20] While the effect on health disappeared, effects on behaviour problems and parenting stress remained after termination of treatment, even though the effects on sleep had disappeared. A possible explanation for this result is that a week of sleep deprivation is too short for behaviour problems to return. The finding that parenting stress was still decreased after treatment termination might be explained by the fact that behaviour problems were also still decreased. Additional analyses showed that there was indeed a significant positive correlation between parenting stress and behaviour problems at the end of the stop week.

Only for sleep latency reported in sleep diaries, there was an effect of behaviour problems at baseline. It appeared that children with more behaviour problems had shorter sleep latency in general. There was no interaction of behaviour problems with treatment phases on sleep. No impact of behaviour problems at

baseline was found for sleep start reported in sleep diaries, nor for sleep variables measured with actometers. Considering the fact that we only found an effect of behaviour problems on sleep latency reported by parents that was not confirmed by the actometer data, this result is difficult to interpret and requires further investigation. As for none of the sleep variables an interaction effect between behaviour problems and treatment phases was found, it can be concluded that behaviour problems at baseline do not affect the effect of melatonin treatment.

We should note that this study was not a placebo-controlled treatment. Therefore, expectations of parents and children might partly explain the effects of melatonin discontinuation. However, this did not happen for behaviour problems and parenting stress since these effects remained. In addition, our objective data (actometers, DLMO), also showed that the positive effect of melatonin on sleep disappeared. As a review of clinical trials investigating placebo effects shows that placebo does not affect objective continuous outcomes,[31] it is not likely that disappearance of the effects of melatonin should be ascribed to expectation effects. Nevertheless, we recommend to control for expectation effects in future studies.

Another weakness is that only short term effects have been investigated. In addition, we did not include a fourth measurement occasion at the end of the half dose week, because, firstly, we did not want to ask parents to complete the questionnaires three times in two weeks, and, secondly, we did not expect to find such short time effects. A final limitation of this study is that all children had to halve the dose in the half dose week, regardless of the dose they were using. For some children this decrease may have been too large.

In the present study, four children did not start again with melatonin treatment because parents were satisfied with the sleep of their child in the stop week. It is unclear to us why these children could stop and others could not. It would be interesting for a future study to investigate possible predictors of treatment duration.

What we learned from this study is that discontinuation of short term melatonin use generally leads to disappearance of the positive effects on sleep. From these findings it is difficult to understand why such a practice existed in the first place. However, a lower dose after melatonin use still seems effective for most children. Clinicians may advise their patients to try a lower dose after they successfully used melatonin for a few weeks. Based on the results of this study, we would advise against complete termination of melatonin use after four weeks of treatment.

REFERENCES

1. Paavonen EJ, Aronen ET, Moilanen I, et al. Sleep problems of school-aged children: a complementary view. Acta Paediatr. 2000;89:223-228.
2. Spruyt K, O'Brien LM, Cluydts R, Verleye GB, Ferri R. Odds, prevalence and predictors of sleep problems in school-age normal children. J Sleep Res. 2005;14:163-176.
3. Fricke-Oerkermann L, Plück J, Schredl M, et al. Prevalence and course of sleep problems in childhood. Sleep. 2007;30:1371-1377.
4. Roberts RE, Roberts CR, Duong HT. Chronic insomnia and its negative consequences for health and functioning of adolescents: A 12-month prospective study. J Adolesc Health. 2008;42:294-302.
5. Meijer AM, Reitz E, Deković M, van den Wittenboer GLH, Stoel RD. Longitudinal relations between sleep quality, time in bed and adolescent problem behaviour. J Child Psychol Psychiatry. 2010;51:1278:1286.
6. Meijer AM. Chronic sleep reduction, functioning at school and school achievement in preadolescents. J Sleep Res. 2008;17:395-405.
7. Meijer AM, van den Wittenboer GLH. The joint contribution of sleep, intelligence and motivation to school performance. Pers Individ Dif. 2004;37:95-106.
8. Brzezinski A. Melatonin in humans. N Engl J Med. 1997;336:186-195.
9. Archer SN, Robilliard DL, Skene DJ, et al. A length polymorphism in the circadian clock gene per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep. 2003;26:413-415.
10. Bjorvatn B, Pallesen S. A practical approach to circadian rhythm sleep disorders. Sleep Med Rev. 2009;13:47-60.
11. Van der Heijden KB, Smits MG, van Someren EJW, Ridderinkhof R, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in adhd and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry. 2007;46:233-241.
12. Ross C, Davies P, Whitehouse W. Melatonin treatment for sleep disorders in children with neurodevelopmental disorders: an observational study. Dev Med Child Neurol. 2002;44:339-344.
13. Smits MG, van Stel HF, van der Heijden KB, Meijer AM, Coenen AML, Kerkhof GA. 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.
14. Carr R, Wasdell MB, Hamilton D, et al. Long-term effectiveness outcome of melatonin therapy in children with treatment-resistant circadian rhythm sleep disorders. J Pineal Res. 2007;43:351-359.
15. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res. 2009;47:1-7.
16. Arendt J. Safety of melatonin in long-term use (?) J Biol Rhythms. 1997;12:673-681.
17. Trienekens N. Longitudinaal effectonderzoek naar kortdurende melatoninebehandeling bij kinderen met chronische inslaap-

problemen. Unpublished master's thesis, University of Amsterdam, Amsterdam, The Netherlands, 2008.

18. Bell BG, Belsky J. Parents, parenting, and children's sleep problems: Exploring reciprocal effects. Br J Dev Psychol. 2008;26:579-593.
19. Hayama J, Adachi Y. Parenting and sleep of mothers in relation to their infant's sleep. Sleep Biol Rhythms. 2007;5:153-155.
20. Meltzer LJ, Mindell JA. Relationship between child sleep disturbances and maternal sleep, mood, and parenting stress: A pilot study. J Fam Psychol. 2007;21:67-73.
21. Sadeh A, Acebo C. The role of actigraphy in sleep medicine. Sleep Med Rev. 2002;6:113-124.
22. Pandi-Perumal SR, Smits M, Spence W, et al. Dim light melatonin onset (DLMO): A tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1-11.
23. Stein REK, Jessop DJ. Functional Status II(R): A measure of child health status. Med Care. 1990;28:1041-1055.
24. Post MWM, Kuyvenhoven MM, Verheij TJM, de Melker RA, Hoes AW. De Nederlandse 'Functional Status II (R)': een vragenlijst voor het meten van de functionele gezondheidstoestand van kinderen. Ned Tijdschr Geneeskd. 1998;142:2675-2679.
25. Achenbach TM. Manual for the Child Behavior Checklist and 1991 Profile. Burlington: University Associates in Psychiatry, 1991.
26. Verhulst FC, van der Ende J, Koot HM. Handleiding voor de CBCL/ 4-18. Erasmus University Rotterdam, The Netherlands, 1996.
27. De Brock AJLL, Vermulst AA, Gerris JRM, Abidin RR. Nijmeegse ouderlijke stress index: meetinstrument voor de vaststelling van stress bij opvoeders: een uitgebreide versie (NOSI) voor psychodiagnostische doeleinden en een verkorte versie (NOSIK) voor signaleringsdoeleinden. Lisse, The Netherlands: Swets & Zeitlinger, 1992.
28. PASW Statistics 17.0. Chicago: SPSS Inc, 2009.
29. Snijders TAB, Bosker RJ. Multilevel analysis: an introduction to basic and advanced multilevel modeling. London: Sage, 1999.
30. PASW Statistics 17.0. Command Syntax Reference, 2009.
31. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med. 2001;344:1594-1602.