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

Effects on sleep, cognition, health, and psychosocial functioning

van Maanen, A.

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CHAPTER 3

Melatonin and sleep effects on health, behaviour problems and parenting stress

THIS IS THE PEER REVIEWED VERSION OF THE FOLLOWING ARTICLE:

Van Maanen, A., Meijer, A. M., Smits, M. G., & Oort, F. J. (2011). Melatonin and sleep effects on health, behavior problems and parenting stress. *Sleep and Biological Rhythms*, 9, 165-171, which has been published in final form at <http://onlinelibrary.wiley.com/doi/10.1111/j.1479-8425.2011.00502.x/full>.

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ABSTRACT

In children with chronic sleep onset insomnia and delayed Dim Light Melatonin Onset, melatonin treatment not only improves sleep but also health, behaviour and parenting stress. The aim of the present study was to see whether the latter effects are dependent on the direct effects on sleep. Data come from 41 children (24 boys, 17 girls; mean age = 9.43 years). They entered melatonin treatment (1 – maximum 5 mg per day) for three weeks, then discontinued treatment by first taking a half dose for one week, and then stopped completely for another week. Sleep was measured with sleep diaries filled in by parents and with actometers. We found a positive effect of actual sleep duration on health but this disappeared after discontinuing treatment. We also found that melatonin treatment decreased behaviour problems, which effect appeared to be stronger for children with an earlier Dim Light Melatonin Onset. These results show that the melatonin effects on health and behaviour problems may partly be dependent on sleep.

INTRODUCTION

Melatonin is an effective treatment for sleep onset problems associated with delayed Dim Light Melatonin Onset (DLMO). Studies report positive effects on sleep in both adults¹⁻⁴ and children.⁵⁻⁷ In addition to the effects on sleep, effects on health, behaviour and parenting stress are found.^{7,8} An important question concerning the effectiveness of melatonin is whether melatonin has a direct effect on these outcomes or whether the effect of melatonin is dependent on (improved) sleep.

Literature shows evidence for melatonin having an inhibiting effect on cancer growth^{9,10} and reducing side effects and increasing efficacy of different kinds of drugs¹¹ and antioxidant effects, through which it could postpone the progression of certain diseases.^{12,13} In addition, melatonin is found to influence mood² and to be negatively related to mood disorders.^{14,15} For example, Cavallo *et al.*¹⁴ found that melatonin secretion was lower in children with depression. However, it is not very clear what this lower melatonin level means. It could implicate that melatonin has a direct influence on (mental) health, but it could also be interpreted as a marker of a lower amplitude circadian output of the clock, thus making individuals more susceptible to phase shifting and instable rhythms, and psychopathology.

Some studies ascribe the beneficial effect of melatonin to improvement of sleep.^{7,16} Rahman *et al.*,¹⁷ who conducted a randomised placebo-controlled trial to investigate the effects of melatonin on depression, suggest that the positive effect of melatonin on depression might be mediated by the phase advance of the circadian rhythm. We assume that relationships between sleep and children's health and behaviour problems and parenting¹⁸⁻²¹ may be explained by a chain of causal effects, where changes in sleep, due to melatonin treatment, in turn cause changes in behaviour, health and parenting stress. In this respect, distinguishing between several aspects of sleep, such as sleep duration or sleep quality appears important in explaining differential effects of sleep on problem behavior.²⁰

In a recent study investigating the effects of termination of short term melatonin treatment in children with chronic sleep onset insomnia, we found positive effects of melatonin on health and behaviour of children and parenting stress in parents. In this study children took melatonin for three weeks and then discontinued treatment by first taking a half dose for one week and then stopping completely for another week. While the effect on health disappeared after treatment discontinuation, the effects on behaviour problems and parenting stress remained.⁸ The research question we aim to answer in the present study

is whether the effect of melatonin on health, behaviour and parenting stress is dependent on sleep. Or, in line with the suggestion of Rahman *et al.*,¹⁷ is the effect of melatonin on these variables dependent on DLMO?

We consider changes in health, behaviour problems and parenting stress after improvement of sleep and we distinguish between different aspects of sleep. Data of 41 children with chronic sleep onset insomnia, who participated in our previous study⁸ investigating the effects of termination of short term melatonin treatment, were used. To our knowledge, there are no studies investigating to what extent effects on sleep moderate the melatonin effects on other outcomes.

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 disorders. 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 of the children completed 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.^{5,7}

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 per day. 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 was further increased 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.

The study 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 we expected it to be too great a burden for parents to complete this extensive questionnaire three times in such a short period.⁸

As the questionnaires and the DLMO measurements have only been administered three times, one of which is before the start of treatment, it was important to also include some information about sleep before treatment. We therefore asked the parents to report the regular bed and sleep time of the child before the start of the study. We used these data only for analyses with the sleep diary data, because these are also parent-reported data.

Measures

Sleep

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 and sleep start were used as sleep parameters in the analyses. Actometers were used to obtain objective information about sleep latency, sleep start, actual sleep duration and sleep efficiency. We decided to use both objective and subjective measures of sleep as research has shown that these give different results.²²⁻²⁵

Dim Light Melatonin Onset

Dim Light Melatonin Onset 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. 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).^{26,27} 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 (2) "almost always". A higher score indicates a better functional status and a better health. Cronbach's alpha's 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).^{28,29} The CBCL is a comprehensive (112 items) questionnaire. The response scale ranged from (0) "not true" to (2) "very true or often true", with a higher score indicating more behaviour problems. The reliability varied from .95 to .96.

Parenting stress

Parenting stress was measured with the Nijmegen Parental Stress Index short version (NOSIK).³⁰ 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, treating the repeated observations as nested within children. For each outcome variable, it was first determined which longitudinal structure described the variances and covariances best³¹ (diagonal for health and behaviour problems, and first-order autoregressive for parenting stress).

Melatonin treatment effects were tested by comparing the fit of models with and without separate parameters for measurement occasions. If the fit improved, main effects of sleep or DLMO and interaction effects of treatment and sleep, or treatment and DLMO were added to the models to test moderation. If model fit improved again, significant effects were interpreted. Significant interaction effects indicate that treatment effects on health, behaviour problems or parenting stress are dependent on the specific sleeping behaviour or DLMO (i.e., are moderated by sleep / DLMO). To facilitate interpretation, all variables have been standardised,³² so that the parameter estimates can be interpreted as effect sizes. In order to illustrate the interaction effects, we plotted expected scores on the dependent variable at the different measurement occasions for different cases, that is, in case a child has an average score on the specific sleeping behaviour or DLMO, in case a child has a high score (1 standard deviation above the mean) on this sleeping behaviour or DLMO, and in case a child has a low score (1 standard deviation below the mean) on the specific sleeping behaviour or DLMO.

RESULTS

Fig. 1 gives an overview of the changes in sleep throughout the study (only actometer data are shown). As can be seen in Fig. 1a, sleep latency does not change much during the first four weeks. However, in the stop week sleep latency increases. Fig. 1b shows that sleep start is somewhat later in the half dose week compared to the treatment weeks, and increases further in the stop week. Actual sleep duration already decreases somewhat in the half dose week whereas sleep efficiency is not very different in the half dose week before deteriorating in the stop week (Fig. 1c and 1d).⁸

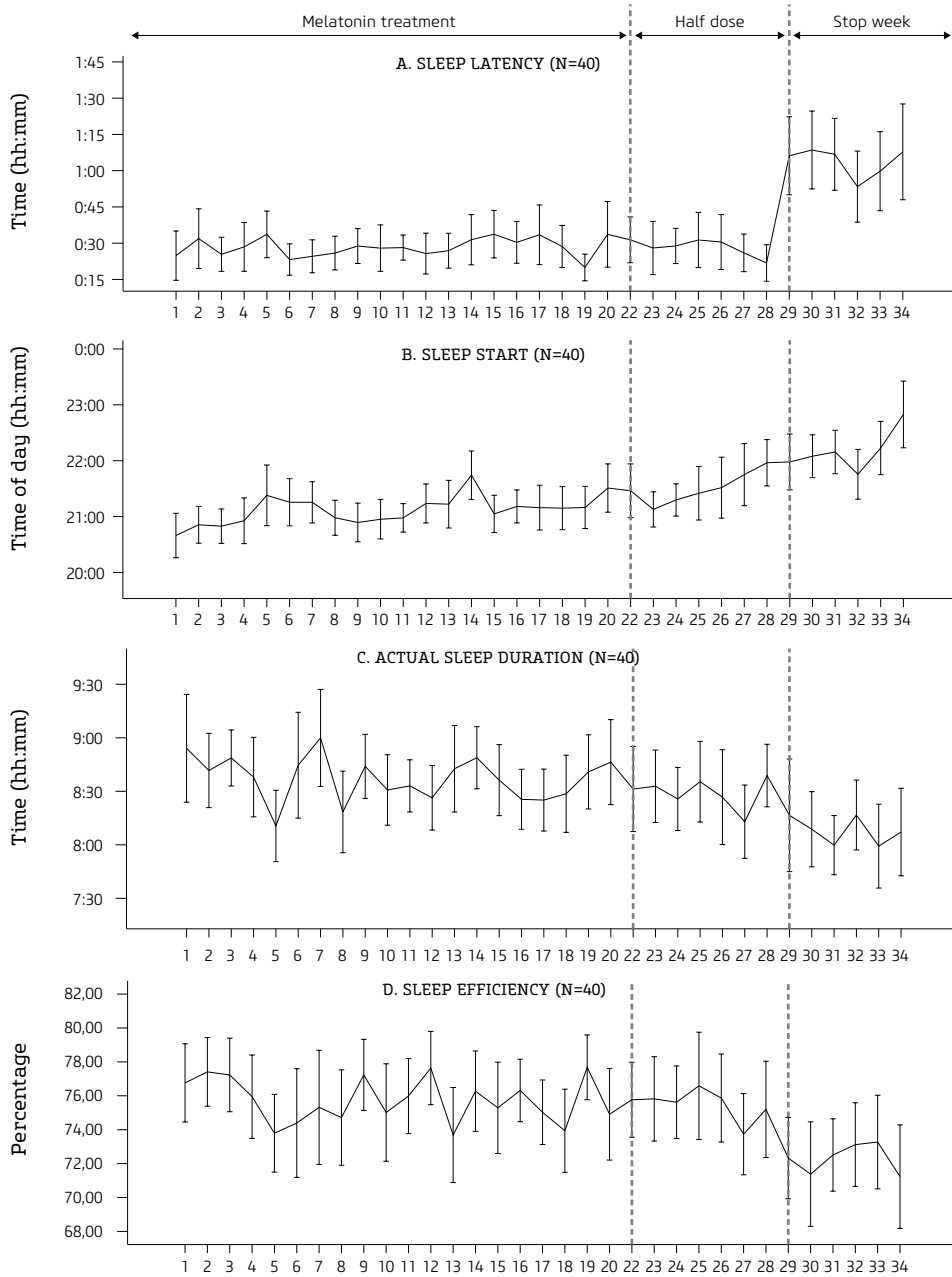


Figure 1. Children's sleep behaviour during and after melatonin treatment (actometer data)
 Day 21 data have been omitted because data collection required many children to stay up late
 (chewing cotton plugs); bars indicate standard errors above and below day averages.

Table 1. Effects of discontinuing melatonin treatment on health as a function of sleep duration

HEALTH	β	S.E.	P
Discontinuation of treatment (T2 vs T1)	-.404	.178	.026
Actual sleep duration	.457	.174	.011
Treatment x Actual sleep duration	-.547	.199	.007

Note: $n = 41$. β , regression coefficient; s.e., standard error.

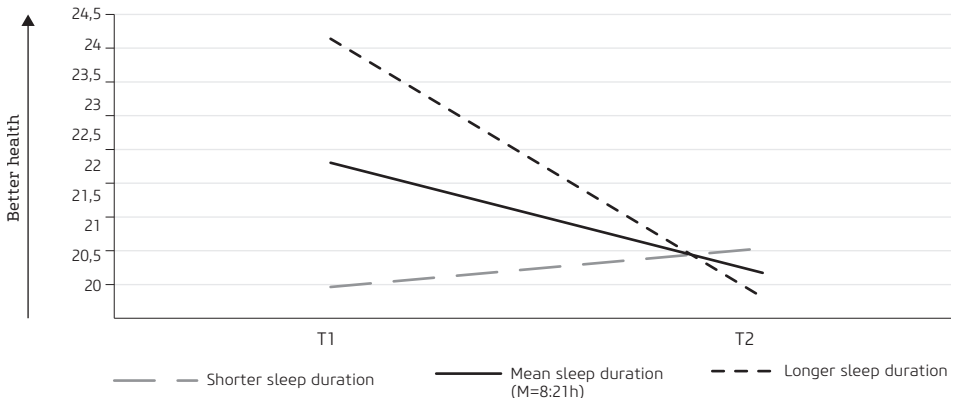


Figure 2. Expected scores on health for children with average, short, and long sleep durations, immediately after melatonin treatment and at the end of the stop week. Health score means are plotted for a child with average sleep duration (8.21 h), short sleep duration (7.32 h, i.e. one standard deviation below average), and long sleep duration (9.10 h, i.e. one standard deviation above average) at t1 (immediately after treatment) and t2 (at the end of the stop week).

Effects of melatonin treatment on health, behaviour problems and parenting stress as a function of sleep and DLMO

For *health*, the main effect of melatonin treatment was significant: health deteriorates from directly after treatment to the end of the stop week. In the next step of the analysis, we also found a significant interaction effect of treatment with actual sleep duration (see Table 1). Immediately after three weeks treatment, health is better for children with longer actual sleep durations than for children with shorter actual sleep durations. However, at the end of the stop week, this effect has disappeared (Fig. 2). In general, longer actual sleep duration is related to better health.

Table 2. Effects of melatonin treatment on behaviour problems as a function of DLMO

BEHAVIOUR PROBLEMS	β	S.E.	P
Treatment effect (T2 vs T0)	-.492	.086	< .001
DLMO	-.110	.112	.331
Treatment x DLMO	.253	.119	.036

Note: $n = 41$. β , regression coefficient; s.e., standard error.

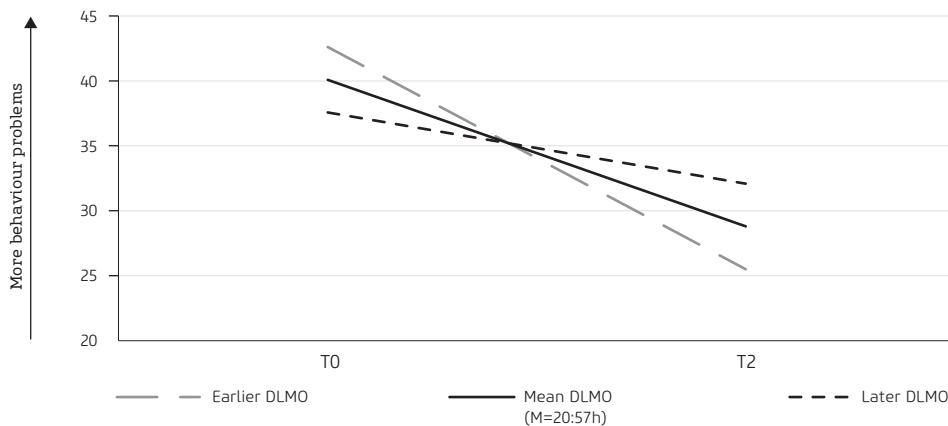


Figure 3. Expected scores on behaviour problems for children with average, early, and late DLMO Scores before melatonin treatment and at the end of the stop week. Behaviour problems score means are plotted for a child with average DLMO (20.57 h), early DLMO (19.59 h, i.e. one standard deviation below average), and late DLMO (21.55 h, i.e. one standard deviation above average) at t0 (before treatment) and t2 (at the end of the stop week).

For *behaviour problems*, a significant treatment effect was found. In the subsequent step, we found a main effect of treatment and an interaction effect of treatment with DLMO. Behaviour problems decreased from baseline to the end of the stop week for all children, and especially for the children with an earlier DLMO (see Table 2 and Fig. 3).

For *parenting stress*, treatment effects were found in the first step of the analysis for the models with sleep diary and DLMO data. The addition of main and interaction effects of sleep and DLMO did not improve model fit. Apparently, sleep variables do not affect the treatment effects on parenting stress.

DISCUSSION

This study found that immediately after three weeks treatment, children with longer actual sleep durations had better health. For these children, there is a strong decrease in health from immediately after treatment to the end of the stop week, whereas this is not the case for children with shorter actual sleep durations. This suggests that the effect of melatonin on health is dependent on actual sleep duration. A possible explanation for this is that children with longer sleep durations had a higher score immediately after treatment. This effect disappeared after discontinuation of melatonin use. This could indicate that longer sleep duration is positively related to a better health, but when sleep duration decreases during the stop week, health also decreases again and is then comparable to the health of children with shorter sleep durations. In general, health scores decreased from directly after treatment to the end of the stop week. In addition, longer sleep duration is related to better health. These findings are supported by research showing the impact of adequate sleep duration on health.³³

Behaviour problems generally decrease from baseline to the end of the stop week. This effect is stronger for children with an earlier DLMO. A possible explanation for this finding is that behaviour problems decrease during melatonin use for all children, but that for children with an earlier DLMO the negative effect of discontinuing melatonin is less strong. As a result, their behaviour problems are not that much affected by discontinuation of treatment in the stop week, whereas for children with later DLMO, behaviour problems increase again from immediately after treatment to the end of the stop week.

The effect of melatonin on parenting stress was not dependent on sleep or DLMO. However, we think that the melatonin treatment of children might affect parenting stress through an improvement of parents' sleep, or through a decrease in children's behaviour problems.

We should note that, since the use of melatonin immediately affects sleep, it is difficult to disentangle the effects of melatonin and sleep. Although studies have shown that fast-release melatonin (used in the present study) affects only sleep latency while controlled-release affects sleep maintenance as well,^{34,35} it is expected that the decrease in sleep latency affects sleep duration. Consequently, the separate effects of melatonin and sleep duration are also difficult to disentangle. We did not take into account the possible effect of diets on the measurement of melatonin. Studies have shown that for instance walnuts³⁶ and other foods, mainly plants,^{37,38} contain melatonin. Intake of these foods could

raise the endogenous melatonin level, and thereby influence the measurement of melatonin. However, as we do not expect that diets of the children changed between the measurement occasions, we do not think our measurements are distorted. Nevertheless, it is advisable for future research to control for possible diet effects when measuring melatonin.

A limitation of the present study is that health, behaviour problems and parenting stress were only measured two or three times. Sleep scores had to be aggregated for the different treatment periods to investigate the interaction effects. A suggestion for future research would be to include daily measurements of psychosocial variables in order to better see any fluctuations. In addition, our sample size was small and we had no real baseline data available for sleep. Daily measurements of psychosocial variables, also measured before beginning melatonin treatment, would be better suited to investigate the fluctuations.

Still, this study yields some interesting insights into the differential effects of melatonin treatment and sleep on health and behaviour problems. Interaction effects were found for objective data (actometers and DLMO). Based on our results, it can be concluded that the effect of melatonin on health and behaviour problems seems to be partly dependent on sleep and DLMO. Future studies should take different aspects of sleep into account when investigating the intriguing relations between sleep and health, behaviour and parenting stress.

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