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

Effects on sleep, cognition, health, and psychosocial functioning

van Maanen, A.

Publication date
2017

Document Version
Other version

License
Other

CHAPTER 7

Cognitive, health and psychosocial effects of melatonin and light therapy in children with chronic sleep onset insomnia

THIS CHAPTER IS BASED ON:

Van Maanen, A., Meijer, A. M., Smits, M. G., van der Heijden, K. B., & Oort, F. J. (2016). Cognitive, health and psychosocial effects of melatonin and light therapy in childhood insomnia.
Manuscript under review.

ABSTRACT

Objectives: *To examine effects of melatonin and light therapy on cognitive, health and psychosocial outcomes in children with chronic sleep onset insomnia; and to disentangle direct effects from indirect effects through sleep improvement.*

Method: *A randomised, double-blind placebo-controlled trial was conducted in which 84 children received melatonin treatment, placebo pills, or light therapy for three to four weeks, after a baseline period of one week. Daily sleep measures were obtained through actigraphy, and children completed cognitive tasks (simple reaction time, visuomotor control, working memory and selective attention) and parents and children completed questionnaires concerning health, mood, school functioning, behavioural and attention problems, at baseline and post-treatment. Regression analyses with bootstrapping were carried out to disentangle direct and indirect (i.e. through sleep) effects.*

Results*: Melatonin treatment improved health and light therapy decreased behaviour problems. Although both treatments improved sleep, the treatment effects on health and behaviour problems were not mediated by sleep.*

Conclusions: *Melatonin and light therapy improved chronic sleep onset problems in children, but fewer effects were found on cognitive, health and psychosocial functioning, and these effects were not mediated by sleep improvement.*

INTRODUCTION

Children with chronic sleep onset insomnia have difficulties falling asleep at the desired clock time. For a subgroup of children this is related to a delay in their biological clock, as indicated by a late Dim Light Melatonin Onset. Due to early school start times, these children do not get sufficient sleep. This may lead to impaired daytime functioning, as there is ample evidence that sleep is related to psychosocial, cognitive and behavioural outcomes in children.[1-3] More specifically, chronic insomnia in adolescents has negative consequences for future health[4] and sleep problems in early childhood are associated with an increased risk of depression/anxiety, attention problems and aggression in adolescence.[3] Furthermore, chronic sleep reduction is associated with worse school functioning and school performance,[5] and impaired performance on cognitive tests.[6]

These negative consequences on different areas of children's functioning call for early treatment of sleep problems. Melatonin is an effective treatment that advances the sleep-wake rhythm and improves various sleep outcomes.[7-12] However, its effects on cognitive, health and psychosocial outcomes are not well understood. There is some evidence that melatonin has positive effects on behaviour problems.[12] Furthermore positive effects of melatonin on health[9] are found. The latter could be related to the influence of melatonin on the immune system and its antioxidant properties.[13] However, melatonin could also indirectly affect these outcomes through improvement in sleep, as sleep is related to health.[4]

Although melatonin is effective in treating chronic sleep onset insomnia in children, optimal treatment duration is not yet known and long-term treatment is sometimes indicated. As there are some concerns about long-term melatonin treatment,[14,15] even though longitudinal studies did not find any harmful effects,[16-18] it is recommendable to investigate potential alternatives for melatonin use in the treatment of chronic sleep onset insomnia with late melatonin onset in children.

Light therapy is an alternative treatment that can improve sleep and possibly cognitive, health and psychosocial outcomes.[19] A recent meta-analysis showed positive effects of light therapy on sleep problems, although most effect sizes were small to medium.[20] Aside from sleep improvement, light therapy has positive effects on mood disorders.[21] The exact working mechanism of bright light therapy in depression remains unclear.[22] Possibly its effects are due to its phase-shifting effect advancing the delayed circadian rhythm occurring in seasonal depression. Another hypothesis is that the direct alerting effect of light plays a

role.[23] However, as light therapy also affects sleep,[20] and sleep disturbances are related to mood and depression,[24] the effect of light therapy on mood might also (partially) be mediated by sleep.

In this study, the effects of melatonin and light therapy on cognitive, health and psychosocial functioning and its underlying mechanisms were investigated by disentangling direct effects of treatment (melatonin or light) from indirect effects through sleep improvement. Earlier we established that both treatments indeed improved sleep, but melatonin effects were stronger.[25] As we hypothesised that effects on cognitive, health and psychosocial outcomes would (partially) be mediated through sleep, we expected that melatonin would have stronger effects on these outcomes.

METHOD

Participants, design, procedure, and treatments have been described earlier.[25] Recapitulating, 84 children (mean age = 10.0 years, SD = 1.5, 61% boys) with chronic sleep onset insomnia and problems with daytime functioning, were randomly assigned to receive melatonin, placebo, or light therapy for three to four weeks, after a baseline period of one week. The study was double-blind for melatonin/placebo. Daily sleep measures were obtained during the whole study period. In addition, children completed cognitive tasks and children and parents completed several questionnaires at baseline and at the end of the treatment period, to measure a range of cognitive, health and psychosocial outcomes. The study was approved by the Medical Ethics Committee of the Academic Medical Centre of the University of Amsterdam, and by the executive board of the hospital.

Melatonin treatment

26 Children (17 boys and 9 girls, mean age = 10.01 years, SD = 1.47, mean DLMO = 21:15 h, SD = 1:02 h) received melatonin treatment. They were instructed to take melatonin tablets (3 mg. fast release, Pharma Nord) at 19:00 h. Five children were diagnosed with AD(H)D and two children with autism spectrum disorder. One child dropped out of the study as he experienced various complaints (joint pains, headache, emotional moods) since using melatonin.

Placebo treatment

28 Children (16 boys and 12 girls, mean age = 10.04 years, SD = 1.63, mean DLMO = 21:00 h, SD = 1:24 h) received placebo treatment. Children were instructed to take the tablets, which looked and tasted identical to the melatonin tablets, at

19:00 h. Six children were diagnosed with ADHD, one child with autism spectrum disorder, and two children with both disorders. One child dropped out as the parents did not want to wait longer for melatonin treatment.

Light therapy

30 Children (18 boys and 12 girls, mean age = 10.08 years, SD = 1.49, mean DLMO = 21:03 h, SD = 1:07 h) received daily light therapy with bright blue-green light (500 nm peak, 8000 lux; Feel Bright Light, Physician Engineered Products Inc.) during 30 minutes between 6:00-8:00 h. Lights were fixed to a cap. Eight children were diagnosed with AD(H)D, one child with autism spectrum disorder, and two children with both disorders. Two children dropped out of the study, one child as participation was experienced too burdensome by the parents, and another child as he experienced headache when using the light cap.

Measures

Sleep

Sleep was assessed with AW4 actiwatches (Cambridge Neurotechnology Ltd, Cambridge, UK).[25]

Cognitive tests

Children completed three cognitive tests of the Amsterdam Neuropsychological Tasks program[26] on a laptop, during the visits to the hospital.

The *Baseline Speed* task measures simple reaction time. Children saw a cross in the middle of the screen, and were asked to press the mouse button as soon as this cross changed into a square. After pressing the button the square disappeared and changed to a cross again, which changed back to a square at 500-2500 milliseconds after pressing the mouse button. The task consists of 32 trials for both index fingers. The mean reaction time over both hands was used as variable in the analysis.

The *Pursuit* task measures the quality of visuomotor control. The child had to follow a randomly moving target (asterisk) at a constant speed of 10 mm/s, first with the non-dominant hand and then with the dominant hand. The average distance (over both hands) with which the child followed the target with the mouse, was used as variable in the analysis.

The task *Memory Search Letters* measures working memory and selective attention. Children had to detect memorised target letters among four letters that were presented in the middle of the screen, and were asked to indicate with the mouse button whether the target letter was shown. The memory load was

increased across three parts, as in the second part there were two target letters and in the third part there were three target letters. Target letters in non-target trials act as distracters. The following outcome parameters were used in the analysis: working memory, operationalised as the change in performance (based on a combination of proportion correct responses and reaction time) from part 1 to part 3, and distractibility, which was operationalised as the difference in performance between part 3 trials with no distracters and trials with 2 distracters. Lower scores indicate better working memory and less distractibility.

Child-report questionnaires

School functioning was measured with the following scales: self-efficacy (6 items),[27] school investment (7 items),[28] relationships with classmates (5 items),[29] relationship with the teacher (5 items).[29] Questions had to be answered on a 5-point scale ranging from '(almost) never / not at all true' to '(almost) always / very true'. A higher score indicates more self-efficacy / school investment, or better relationships with classmates or the teacher. Cronbach's alpha varied from .63 to .81 for the different scales at the two measurement occasions separately.

The Positive and Negative Affect Scale for Children[30] was used to measure *positive and negative affect*. Children had to indicate on a five-point scale (ranging from 'very slightly or not at all' to 'extremely') to what extent they had experienced 30 feelings/emotions in the past few weeks. Two scores can be derived from this questionnaire: a total score for positive affect, and a total score for negative affect, with higher scores indicating more positive / negative affect respectively. For positive affect, Cronbach's alpha was .67 at baseline and .79 after treatment, and for negative affect Cronbach's alpha's were .83 and .82.

Children completed the *attention problems* scale from the Youth Self Report.[31] This scale consists of nine items, asking children about how they acted in the past month. Response categories varied from 'not true' to 'very true or often true', with a higher score indicating more attention problems. Cronbach's alpha was .72 at baseline and .80 post-treatment.

Parent-report questionnaires

Children's *health status* was measured with the first part of the Functional Status II-R.[32] consisting of 14 items measuring parent-reported health of their child during the past week. Parents have to indicate how often their child showed certain behaviours, on a three-point scale ranging from 'never or rarely' to 'almost always'. A higher score indicates a better health status. Cronbach's alpha was .80 at baseline and .79 after treatment.

Parents reported about their child's *behaviour problems* with the Strength and Difficulties Questionnaire.[33] This questionnaire consists of 25 items and five subscales, but we only used the total behaviour problems scale. Parents indicate how often their child showed certain behaviours on a three-point scale, ranging from 'not true' to 'certainly true'. A higher score indicates more behaviour problems. Cronbach's alpha was .80 at baseline and .85 after treatment.

Inhibitory control was measured with the inhibitory control scale of the Early Adolescent Temperament Questionnaire-Revised.[34] Parents completed five items about their child's capacity to plan and to suppress inappropriate responses on a five-point scale. Response categories varied from 'almost always untrue' to 'almost always true'. A higher score represents better inhibitory control. Cronbach's alpha was .74 at baseline and .72 post-treatment.

Analyses

After data screening, the expectation maximization imputation procedure[35]was used to substitute missing values for the cognitive, health, and psychosocial measures. We did not impute data when an entire measurement occasion (baseline or post-treatment) was missing for the child- or parent-report data. For the sleep variables, we calculated averages for the baseline days and for the treatment days using all available actigraphy data. We did not use an imputation procedure for the sleep data if some days were missing, as averages could still be calculated based on the available days for the individual child. All continuous variables were standardised, to enable the comparison of regression coefficients.

In order to investigate direct and indirect effects of melatonin treatment and light therapy on cognitive, health and psychosocial outcomes, we carried out regression analyses, using bootstrapping to estimate standard errors and confidence intervals.[36] This method enables to examine both direct and indirect effects of the independent variable on the dependent variable, without necessarily assuming that the independent variable must directly affect the dependent variable when the mediating variable is excluded.[37] We applied two-sided tests with an alpha of 10% to increase power.

We used change in sleep onset time and total sleep time (calculated as the mean of treatment days minus the mean of baseline days) as mediator variables, as principal components analysis showed that these two variables together best represented the variance in sleep outcomes. As dependent variables we used the change in cognitive, health and psychosocial outcomes (calculated as post-treatment minus baseline score). Independent variables were indicator variables for melatonin treatment (versus placebo treatment) and light therapy (also versus

placebo treatment).

The analyses were carried out with the two mediators simultaneously, separately for all outcome measures. In this way, we were able to examine two direct effects (of the two treatments on the specific outcome measure), four indirect effects (of the two treatments through both mediators), and the total effects (i.e. direct as well as indirect effects), as well as melatonin and light effects on the sleep variables and sleep effects on the outcome measures (see Figure 1 for a schematic overview of all effects).

We checked for outliers, but as results did not change after removing outliers, except for one outcome reported below, we report the results for all available data.

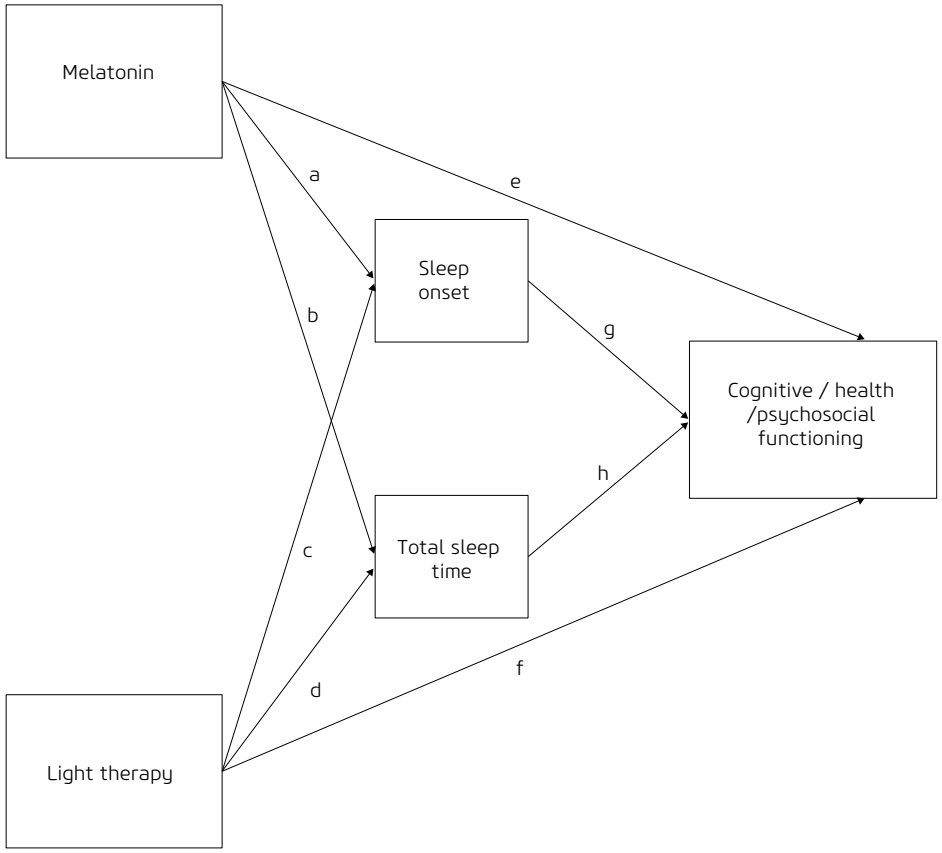

Figure 1. Schematic overview direct and indirect effects

RESULTS

Total sleep time increased significantly after melatonin treatment and light therapy, and melatonin significantly advanced sleep onset time (Tables 1, 2, 3). The effects on the cognitive, health and psychosocial outcomes are described below.

Cognitive outcomes

No significant direct effects of treatment on cognitive outcomes were found (Table 1). There were no significant direct effects of advanced sleep onset time or total sleep time on cognitive outcomes either. However, we did find indirect effects of melatonin treatment and light therapy on working memory through total sleep time, indicating that working memory deteriorated after treatment. These indirect effects did not yield significant total effects. When we repeated the analyses after removal of outliers, the indirect effect of melatonin was no longer significant.

Child-report outcomes

There was a direct effect of light therapy on school investment, indicating that school investment decreased after light therapy (Table 2). In addition, there was a direct effect of total sleep time on school investment (a longer sleep duration was associated with an increase in school investment). Indeed, both light therapy and melatonin indirectly increased school investment through an increase in total sleep time. There was a direct effect of sleep onset time on attention problems (an earlier sleep onset time was associated with a decrease in attention problems), and melatonin indirectly decreased attention problems, and increased positive affect, through an advance in sleep onset time. Both melatonin and light therapy indirectly increased negative affect, through an increase in total sleep time. However, the effects mentioned above did not result in significant total effects of the treatments on any of the child-report outcomes.

Parent-report outcomes

There was a direct effect of light therapy on behaviour problems, indicating that behaviour problems decreased after light therapy (Table 3). However, melatonin and light therapy indirectly increased behaviour problems through total sleep time. These effects were smaller, and the total effect of light on behaviour problems was still significant and in the expected direction. There was also a direct effect of melatonin on health, resulting in a significant total effect, indicating that health improved after melatonin treatment. Melatonin and light therapy

indirectly increased inhibitory control through an advance in sleep onset time, but this did not result in significant total effects.

Table 1. Direct and indirect effects of melatonin treatment and light therapy on cognitive outcomes

	SLEEP ONSET TIME			
TREATMENT EFFECTS ON SLEEP OUTCOMES	β	90% CI		
Effect melatonin (a)	**-1.17**	**[-1.60,-.74]**		
Effect light therapy (c)	-.31	[-.72,.09]		
	Reaction time Baseline Speed task		Distance Pursuit Task	
EFFECTS ON COGNITIVE OUTCOMES	β	90% CI	β	90% CI
Direct effects				
Direct effect melatonin (e)	-.15	[-.72,.41]	-.12	[-.68,.45]
Direct effect light (f)	.11	[-.38,.60]	-.06	[-.55,.44]
Effect SOT (g)	-.11	[-.34,.12]	-.01	[-.24,.22]
Effect TST (h)	.06	[-.16,.27]	-.08	[-.30,.13]
Indirect effects				
Indirect effect melatonin through SOT (a*g)	.13	[-.10,.47]	.01	[-.21,.23]
Indirect effect light through SOT (c*g)	.04	[-.01,.18]	.00	[-.06,.09]
Indirect effect melatonin through TST (b*h)	.05	[-.09,.24]	-.07	[-.28,.08]
Indirect effect light through TST (d*h)	.04	[-.08,.20]	-.06	[-.24,.07]
Total effects				
Total effect melatonin (e + a*g + b*h)	.03	[-.46,.51]	-.17	[-.66,.32]
Total effect light (f + c*g + d*h)	.19	[-.27,.65]	-.11	[-.57,.35]

Note: β = standardised regression coefficient; 90% CI = 90% confidence interval; SOT = sleep onset time; TST = total sleep time. The letters between brackets in the first column refer to the paths in Figure 1. Significant effects are indicated in bold*. Sample sizes in the analyses with cognitive outcomes are N = 23 (melatonin), N= 26 (placebo), and N = 28 (light therapy).*

TOTAL SLEEP TIME			
		β	90% CI
Effect melatonin (b)		**.80**	**[.35,1.26]**
Effect light therapy (d)		**.68**	**[.25,1.12]**
Working memory Memory Search Letters Task		Distractibility Memory Search Letters Task	
β	90% CI	β	90% CI
-.25	[-.81,.30]	.14	[-.42,.71]
-.40	[-.88,.08]	.03	[-.46,.52]
-.07	[-.30,.15]	-.09	[-.32,.14]
.17	[-.05,.38]	.02	[-.20,.23]
.09	[-.21,.58]	.10	[-.22,.66]
.02	[-.04,.22]	.03	[-.04,.26]
.13	**[.02,.34]**	.01	[-.13,.22]
.11	**[.02,.31]**	.01	[-.11,.19]
-.03	[-.52,.45]	.26	[-.23,.74]
-.26	[-.72,.20]	.07	[-.39,.54]

Table 2. Direct and indirect effects of melatonin treatment and light therapy on child reported outcomes

	SLEEP ONSET TIME	
TREATMENT EFFECTS ON SLEEP OUTCOMES	β	90% CI
Effect melatonin (a)	**-1.22**	**[-1.71,-.73]**
Effect light therapy (c)	-.26	[-.72,.20]

	Self-efficacy		School investment	
EFFECTS ON CHILD-REPORT OUTCOMES	β	90% CI	β	90% CI
Direct effects				
Direct effect melatonin (e)	.11	[-.55,.77]	-.31	[-.92,.30]
Direct effect light (f)	.05	[-.51,.60]	**-.52**	**[-1.04,-.01]**
Effect SOT (g)	-.10	[-.36,.16]	-.10	[-.34,.14]
Effect TST (h)	-.02	[-.26,.22]	**.33**	**[.11,.55]**
Indirect effects				
Indirect effect melatonin through SOT (a*g)	.12	[-.13,.54]	.13	[-.09,.42]
Indirect effect light through SOT (c*g)	.03	[-.02,.21]	.03	[-.01,.15]
Indirect effect melatonin through TST (b*h)	-.02	[-.24,.24]	**.31**	**[.08,.66]**
Indirect effect light through TST (d*h)	-.01	[-.17,.19]	**.24**	**[.06,.56]**
Total effects				
Total effect melatonin (e + a*g + b*h)	.22	[-.34,.77]	.12	[-.43,.67]
Total effect light (f + c*g + d*h)	.06	[-.46,.58]	-.26	[-.77,.26]

Note: β = standardised regression coefficient; 90% CI = 90% confidence interval; SOT = sleep onset time; TST = total sleep time. The letters between brackets in the first column refer to the paths in Figure 1. Significant effects are indicated in **bold**. *Sample sizes in the analyses with child-report outcomes are N = 18 (melatonin), N= 20 (placebo), and N = 23 (light therapy).*

	TOTAL SLEEP TIME	
	β	90% CI
Effect melatonin (b)	.92	[.39,1.45]
Effect light (d)	.71	[.21,1.21]

Relationships with classmates		Relationship with the teacher		Positive affect		Negative affect		Attention problems	
β	90% CI	β	90% CI	β	90% CI	β	90% CI	β	90% CI
.06	[-.59,.72]	-.49	[-1.14,.16]	-.61	[-1.26,.03]	.18	[-.45,.82]	.14	[-.48,.76]
.32	[-.23,.87]	-.42	[-.97,.13]	-.10	[-.64,.44]	.22	[-.32,.75]	.24	[-.29,.76]
-.06	[-.32,.19]	-.13	[-.38,.13]	-.20	[-.45,.06]	-.07	[-.32,.18]	**.27**	**[.02,.51]**
-.05	[-.29,.19]	.07	[-.16,.31]	-.07	[-.30,.16]	.21	[-.02,.44]	.06	[-.16,.29]
.08	[-.28,.50]	.15	[-.09,.51]	**.24**	**[.02,.59]**	.09	[-.18,.48]	**-.33**	**[-.76,-.02]**
.02	[-.05,.21]	.03	[-.02,.19]	.05	[-.01,.23]	.02	[-.03,.20]	-.07	[-.32,.02]
-.05	[-.30,.14]	.07	[-.06,.27]	-.06	[-.32,.13]	**.20**	**[.04,.52]**	.06	[-.15,.24]
-.04	[-.23,.10]	.05	[-.04,.22]	-.05	[-.22,.10]	**.15**	**[.02,.44]**	.04	[-.11,.19]
.10	[-.45,.64]	-.27	[-.82,.28]	-.44	[-.99,.11]	.47	[-.08,1.01]	-.13	[-.67,.41]
.30	[-.22,.81]	-.34	[-.85,.18]	-.10	[-.62,.42]	.39	[-.13,.90]	.21	[-.29,.72]

Table 3. Direct and indirect effects of melatonin treatment and light therapy on parent reported outcomes

	SLEEP ONSET TIME	
TREATMENT EFFECTS ON SLEEP OUTCOMES	β	90% CI
Effect melatonin (a)	**-1.22**	**[-1.67,-.77]**
Effect light therapy (c)	-.37	[-.80,.06]
	Health status	
EFFECTS ON PARENT-REPORT OUTCOMES	β	90% CI
Direct effects		
Direct effect melatonin (e)	**.72**	**[.19,1.25]**
Direct effect light (f)	.24	[-.23,.70]
Effect SOT (g)	-.19	[-.40,.02]
Effect TST (h)	.01	[-.18,.21]
Indirect effects		
Indirect effect melatonin through SOT (a*g)	.23	[-.03,.61]
Indirect effect light through SOT (c*g)	.07	[-.01,.27]
Indirect effect melatonin through TST (b*h)	.01	[-.13,.20]
Indirect effect light through TST (d*h)	.01	[-.10,.19]
Total effects		
Total effect melatonin (e + a*g + b*h)	**.96**	**[.50,1.42]**
Total effect light (f + c*g + d*h)	.32	[-.12,.76]

Note: β = standardised regression coefficient; 90% CI = 90% confidence interval; SOT = sleep onset time; TST = total sleep time. The letters between brackets in the first column refer to the paths in Figure 1. Significant effects are indicated in bold. *Sample sizes in the analyses with parent-report outcomes are N = 23 (melatonin), N= 23 (placebo), and N = 27 (light therapy).*

TOTAL SLEEP TIME			
		β	90% CI
Effect melatonin (b)		**.82**	**[.34,1.30]**
Effect light therapy (d)		**.73**	**[.26,1.19]**
Behaviour problems		Inhibitory control	
β	90% CI	β	90% CI
-.54	[-1.10,.03]	-.49	[-1.06,.09]
-.65	**[-1.15,-.16]**	-.07	[-.57,.43]
-.06	[-.28,.17]	-.21	[-.43,.02]
.17	[-.04,.38]	.01	[-.21,.22]
.07	[-.22,.34]	**.25**	**[.05,.55]**
.02	[-.05,.14]	**.08**	**[.004,.23]**
.14	**[.004,.38]**	.00	[-.17,.16]
.12	**[.005,.34]**	.00	[-.15,.14]
-.33	[-.82,.16]	-.23	[-.73,.27]
-.51	**[-.98,-.04]**	.01	[-.47,.49]

DISCUSSION

In this study we investigated direct effects of melatonin and light therapy on various cognitive, health and psychosocial outcomes, and indirect effects on these outcomes through sleep. Although melatonin and light therapy increased total sleep time and melatonin advanced sleep onset time, we did not find effects of those sleep variables on the cognitive outcomes or parent-report outcomes, and only two effects on child-report outcomes. We found three direct effects of melatonin and light therapy on child-report and parent-report outcomes. Altogether, only two total effects (i.e. total of direct and indirect effects) were significant, indicating that health improved after melatonin treatment and behaviour problems decreased after light therapy.

With regard to the mechanisms underlying these effects, the hypothesis that the effects of melatonin and light therapy on health and behaviour problems would be caused by improved sleep, was not supported by our data. Instead, the two total effects seemed to be caused by direct effects of the treatments. The improvement in health after melatonin treatment is in line with research showing that melatonin has antioxidant properties[38,39] and beneficial effects on the immune system.[13] Although we are unaware of studies showing effects of light therapy on behaviour problems in children or adolescents, this finding is in accordance with research showing a reduction in behaviour problems in elderly persons with dementia after light therapy.[40]

Apart from these two total effects, there were several significant direct and indirect effects. Melatonin and light therapy indirectly increased behaviour problems through total sleep time. This was contrary to our expectations, and also in contrast to the (stronger) direct effect of light which led to a decrease in behaviour problems. That a longer sleep duration is related to more behaviour problems is counterintuitive, but it could be that when children are more rested they become more active and display more boisterous behaviour, which can be interpreted as externalising behaviour problems. However, it should be noted that the effects were just borderline significant.

Melatonin and light therapy had small indirect negative effects on working memory through an increase in total sleep time, although the effect of melatonin disappeared after removing outliers. No further effects on cognitive functioning were found. This was contrary to what we expected, but similar to a previous study that found no effects on cognitive outcomes in children after melatonin treatment.[10] In that study the lack of effects was explained by the lack of large improvements in sleep and the possibility that the treatment was too short

(four weeks), which could have been the case in our study as well. However, contrary to Van der Heijden et al.,[10] we did find an effect of melatonin on attention problems. A third explanation that they offered for the lack of effects was that effects were possibly masked by cognitive deficits of children with ADHD. However, the results of our study show that effects are also absent in a general sample of children with chronic sleep onset insomnia.

Interestingly, although light therapy had a direct negative effect on school investment, both treatments indirectly increased school investment through an increase in total sleep time. The latter effects are explainable by the fact that children have more energy when they are well-rested, and may therefore be more motivated to work hard in school. This is supported by research showing a relation between sleep quality and 'eagerness' in the context of school performance.[41]

Melatonin indirectly decreased attention problems and increased positive affect, through advancing sleep onset time. However, both melatonin and light therapy also led to an increase in negative affect through an increase in total sleep time. These results seem in contrast with each other, although an explanation could be that emotions are experienced stronger when children are well-rested. This is supported by the study of Norlander et al., [42] who also found a relation between good sleep quality and both high positive and high negative affect.

Although several direct and indirect effects of melatonin and light therapy on cognitive, health, and psychosocial outcomes were found, these effects did not result in significant total effects as they were smaller or sometimes opposite to other effects (for example for school investment where the direct effects of melatonin and light therapy were negative but the indirect effects positive). It can therefore be questioned to what extent these effects are clinically relevant when they do not result in overall effects.

The absence of more or stronger indirect effects was due to the absence of effects of sleep on the outcomes (paths g and h in Figure 1), as melatonin and light therapy did significantly affect total sleep time and sleep onset time (although the latter was only true for melatonin). Possibly, the improvements in sleep were too small or the period of improved sleep too short to exert more and stronger effects on the cognitive, health and psychosocial outcomes.

This study has several strengths. To our knowledge, this is the first study directly comparing effects of melatonin and light therapy on sleep and cognitive, health and psychosocial outcomes in children. In addition, we used a double-blind randomised controlled placebo design using multiple informants (child-re-

port, parent-report and objective data). However, our study has also some limitations. Most importantly, although a sample size of 84 is relatively large for a clinical study, we only had 18-28 participants per group in the analyses, yielding insufficient power to find small effects. Our power estimates are about 60% to find medium sized differences and about 90% to find large sized differences between treatment groups when testing at a one-sided 5% level of significance. In addition, as we mentioned previously,[25] we did not advance the timing of light therapy and we had no placebo condition for light therapy. We also did not control for light exposure in the evening, although information about the importance of restricting light in the evening was included in the sleep hygiene instructions that were handed out to all participants. We did not check the effect of the sleep hygiene instructions. However, as treatment was randomised, we do not have reason to believe that children in the light group would have had more exposure to evening light than children in the other two groups, or that one group would have benefited more from sleep hygiene instructions.[25]

In sum, in this study we investigated the effects of melatonin and light therapy on cognitive, health and psychosocial outcomes, and whether the effects were mediated by sleep improvement or were direct effects. We only found two significant total effects (melatonin improved health, light decreased behaviour problems), and surprisingly, these effects seemed to be direct treatment effects. Overall, melatonin and light therapy were effective treatments for chronic sleep onset problems in children. However, the effects on cognitive, health and psychosocial functioning were smaller, and we did not find evidence to support the idea that these effects were caused by improvement of sleep.

REFERENCES

1. Astill RG, van der Heijden KB, van IJzendoorn MH, van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed. Psychol Bull. 2012;138:1109-1138.
2. Dewald JF, Meijer AM, Oort FJ, Kerkhof GA, Bögels SM. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: a meta-analytic review. Sleep Med Rev. 2010;14:179-189.
3. Gregory AM, O'Connor TG. Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. J Am Acad Child Adolesc Psychiatry. 2002;41:964-971.
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. Chronic sleep reduction, functioning at school and school achievement in preadolescents. J Sleep Res. 2008;17:395-405.
6. De Bruin EJ, van Run C, Staaks J, Meijer AM. Effects of sleep manipulation on cognitive functioning of adolescents: A systematic review. Sleep Med Rev. 2016; doi:10.1016/j.smrv.2016.02.006.
7. Bruni O, Alonso-Alconada D, Besag F, et al. Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol. 2015;19:122-133.
8. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. 2001;16:86-92.
9. Smits MG, van der Heijden K, Meijer AM, Coenen AM, 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.
10. Van der Heijden KB, Smits MG, van Someren EJ, Ridderinkhof KR, 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.
11. Van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep. 2010;33:1605-1614.
12. Van Maanen A, Meijer AM, Smits MG, Oort FJ. Termination of short term melatonin treatment in children with delayed Dim Light Melatonin Onset: effects on sleep, health, behavior problems, and parenting stress. Sleep Med. 2011;12:875-879.
13. Carpentieri A, de Barboza GD, Areco V, López MP, de Talamoni NT. New perspectives in melatonin uses. Pharmacol Res.2012;65:437-444.
14. Kennaway DJ. Paediatric use of melatonin. Eur J Paediatr Neurol. 2015;19:489-490.
15. Kennaway DJ. Potential safety issues in the use of the hormone melatonin in paediatrics. J Paediatr Child Health. 2015;51:584-589.

16. 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.
17. 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.
18. Van Geijlswijk IM, Mol RH, Egberts TC, Smits MG. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. Psychopharmacology. 2011;216:111-120.
19. Bjorvatn B, Pallesen S. A practical approach to circadian rhythm sleep disorders. Sleep Med Rev. 2009;13:47-60.
20. Van Maanen A, Meijer AM, van der Heijden KB, Oort FJ. The effects of light therapy on sleep problems: A systematic review and meta-analysis. Sleep Med Rev. 2016;29:52-62.
21. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry. 2005;162:656-662.
22. Pail G, Huf W, Pjrek E, et al. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology. 2011;64:152-162.
23. Lewy AJ, Sack RL, Singer CM, White DM. The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. Psychopharmacol Bull. 1987;23:349-353.
24. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135:10-19.
25. Van Maanen A, Meijer AM, Smits MG, van der Heijden KB, Oort FJ. Effects of melatonin and bright light treatment in childhood chronic sleep onset insomnia with late melatonin onset: A randomised controlled study. Sleep. 2016; in press.
26. De Sonneville LMJ. Amsterdam Neurpsychological Tasks: a computer-aided assessment program. In: Den Brinker BPLM, Beek PJ, Brand AN, Maarse FJ, Mulder LJM, eds. Cognitive ergonomics, clinical assessment and computer-assisted learning. Lisse: Swets & Zeitlinger; 1999:187-203.
27. Midgley C, Maehr ML, Hruda LZ, et al. Manual for the Patterns of Adaptive Learning Scales (PALS). Ann Arbor, MI: University of Michigan, 2000.
28. Roede E. Explaining student investment, an investigation of high school students' retrospective causal accounts of their investment in school (Academic dissertation). Amsterdam: Stichting Centrum voor Onderwijsonderzoek, Universiteit van Amsterdam; 1989.
29. Peetsma TTD, Wagenaar E, de Kat E. School motivation, future time perspective and well-being of high school students in segregated and integrated schools in the Netherlands and the role of ethnic self-description. In: Koppen JK, Lunt I, Wulf C, eds. Education in Europe, cultures, values, institutions in transition (Vol. 14). Münster, New York: Waxmann; 2001:54-74.

30. Laurent J, Catanzaro SJ, Joiner TE, et al. A measure of positive and negative affect for children: Scale development and preliminary validation. Psychol Assess. 1999;11:326-338.
31. Achenbach TM. Manual for the Youth Self-Report and 1991 profile. Burlington, VT: University of Vermont, Department of Psychiatry, 1991.
32. Stein REK, Jessop DJ. Functional Status II(R): A measure of child health status. Med Care. 1990;28:1041-1055.
33. Goodman R. The Strengths and Difficulties Questionnaire: A research note. J Child Psychol Psychiatry. 1997;38:581-586.
34. Hartman CA, Rothbart MK. Nederlandse vertaling van de Early Adolescent Temperament Questionnaire. Universitair Medisch Centrum Groningen, Disciplinegroep Psychiatrie, Groningen, Nederland, Intern rapport, 2001.
35. IBM SPSS Statistics 22 Command Syntax Reference, 2013.
36. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40:879-891.
37. Hayes AF. Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. Commun Monogr. 2009;76:408-420.
38. Bonnefont-Rousselot D, Collin F. Melatonin: action as antioxidant and potential applications in human disease and aging. Toxicology. 2010;278:55–67.
39. Reiter RJ, Paredes SD, Manchester LC, Tan DX. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. Crit Rev Biochem Mol Biol. 2009;44:175-200.
40. Kim S, Song HH, Yoo SJ. The effect of bright light on sleep and behavior in dementia: an analytic review. Geriatr Nurs. 2003;24:239-243.
41. Meijer AM, van den Wittenboer GL. The joint contribution of sleep, intelligence and motivation to school performance. Pers Ind Diff. 2004;37:95-106.
42. Norlander T, Johansson Å, Bood SÅ. The affective personality: Its relation to quality of sleep, well-being and stress. Soc Behav Personal. 2005;33:709-722.