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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 8

Summary and discussion

CASE ILLUSTRATION

In the Introduction of this thesis Jorrit was mentioned, who had difficulty sleeping on time and problems with concentration and attention at school. Jorrit and his parents eventually visited their general practitioner for his sleep problems. They were referred to a specialised sleep centre where the diagnosis Delayed Sleep Wake-Phase Disorder was made. After determining his DLMO, melatonin treatment was started and was soon found effective. Jorrit now felt sleepy in the evening, and wanted to go to bed by himself. He usually fell asleep within 15 minutes, and woke up by himself in the morning, sometimes even before his alarm clock. After a while he started feeling more rested during the day, and experienced that he could better concentrate at school. His parents felt that they had the 'old Jorrit' back.

Melatonin treatment is known to be an effective treatment for chronic sleep onset problems in children that are related to a late melatonin onset, as it can advance the sleep-wake rhythm and improve sleep.¹⁻⁴ However, it is currently not known how long melatonin treatment should be continued, while especially in young children, short term treatment is favourable over long term treatment.

In this thesis, we looked for alternatives to long term melatonin use, by investigating the consequences of gradual termination of short term melatonin treatment (**Chapter 2**), and applying a classical conditioning experiment to see whether this would help preserving the effects (**Chapter 4**). We also examined light therapy as an alternative treatment to melatonin, first by conducting a meta-analysis about the effects of light therapy on different types of sleep problems (**Chapter 5**), and subsequently by reporting about a randomised controlled trial where the effects of light therapy on sleep onset problems in children were compared to effects of melatonin and a placebo treatment (**Chapter 6**). In addition, we examined direct and indirect effects of melatonin treatment and light therapy on cognition, behaviour and psychosocial functioning (**Chapter 3** and **Chapter 7**).

TERMINATION OF SHORT TERM MELATONIN TREATMENT

In **Chapter 2** we investigated the effects of gradual termination of short term melatonin treatment using an experimental design. Children with chronic sleep onset problems and a late Dim Light Melatonin Onset (DLMO) received melatonin treatment for three weeks, after which they gradually discontinued treatment by first taking a half dose for one week and then stopping completely for another week. We found that DLMO and sleep advanced during treatment, and in addition, there were positive effects on health, behaviour problems and parenting stress. While the latter two remained after the stop week, the effects on health, DLMO and sleep disappeared during the half dose and stop weeks. Therefore, we concluded that termination after four weeks of melatonin treatment is too early.

As **Chapter 2** showed that the positive effects of melatonin treatment disappear after its discontinuation, we explored in **Chapter 4** if classical conditioning could help to preserve treatment effects. Classical conditioning is a learning principle originally described by Pavlov,⁵ in which a stimulus that evokes a certain response is coupled to a neutral stimulus that after a learning process will

evoke the same response. There have been a few case descriptions in the literature where classical conditioning was applied in the treatment of sleep problems,^{6,7} and we applied this in a pilot study by asking children to drink a biological lemonade while taking melatonin, and turning on a dim light red lamp when they went to bed. This procedure was applied during three weeks of treatment, and during a half dose and stop week. Results were similar to those described in Chapter 2, as we found that the positive treatment effects on DLMO, sleep onset problems and health disappeared after treatment discontinuation. However, we found that with classical conditioning sleep latency and sleep start delayed less in the stop week, but this was only true for children without comorbid ADHD or autism. This suggests that there might be a small effect of classical conditioning in preserving effects after treatment discontinuation.

IS LIGHT THERAPY A GOOD ALTERNATIVE TO MELATONIN TREATMENT?

As the previous chapters suggest that melatonin treatment should be continued for a longer time period in order to preserve the positive effects, we wanted to investigate an alternative treatment for sleep onset problems related to a delayed melatonin onset in children, namely light therapy. Bright light can influence the circadian rhythm and has alerting effects,^{8,9} and is recommended treatment for circadian rhythm sleep disorders, such as Delayed Sleep-Wake Phase Disorder (DSWPD).¹⁰⁻¹²

However, studies into light therapy effectiveness had yielded inconsistent results. Therefore, we aimed to give a systematic overview of the available evidence concerning the effects of light therapy on sleep problems by carrying out a meta-analysis (Chapter 5). We included 53 studies with a total of 1154 participants, and calculated overall effects and effects on various sleep parameters, both for specific types of sleep problems (circadian rhythm sleep disorders, insomnia, sleep problems related to Alzheimer's disease and dementia) and sleep problems in general. Furthermore, we examined several moderators to see whether they influenced treatment effects. We found that light therapy was effective in the treatment of circadian rhythm sleep disorders, insomnia, sleep problems related to Alzheimer's disease/dementia, and for sleep problems in general, although most effect sizes were small to medium. We found some moderator effects but these did not show a consistent pattern.

Although our meta-analysis showed promising results for light therapy, the

results were based on studies carried out in adolescents and especially (older) adults, as light therapy had not yet been investigated in children. Therefore, we set up a double-blind placebo-controlled randomised controlled trial in which we compared the effects of light therapy to those of melatonin in children with sleep onset insomnia and late melatonin onset (Chapter 6). We included 84 children that were randomly assigned over three treatment groups: melatonin, placebo pills or light therapy. They received treatment for three to four weeks, during which we obtained daily measures of sleep through sleep diaries completed by parents and actigraphy. The results showed that both treatments positively influenced various sleep outcomes, but melatonin affected more outcomes and its effects were generally stronger. Therefore, we concluded that melatonin would be the preferred treatment for use in clinical practice.

EFFECTS OF SLEEP TREATMENT ON COGNITIVE, HEALTH AND PSYCHOSOCIAL OUTCOMES

As treatment for sleep problems not only aims at improving sleep but also at improving daytime functioning, we also investigated cognitive, health and psychosocial effects of the treatments (Chapter 7). In addition, we wanted to know whether any effects of melatonin and light therapy on measures of daytime functioning were direct effects of the treatments, or indirect effects of sleep improvement. In Chapter 3 we explored this question, and found that sleep duration influenced health, and that the reduction in behaviour problems was stronger for children with an earlier DLMO. These findings suggest that the effects of melatonin on health and behaviour problems were partly dependent on sleep.

We continued the investigation of this research question in Chapter 7, where we disentangled direct and indirect effects of melatonin and light therapy on various cognitive, health and psychosocial outcomes. We found a few direct and indirect effects of the treatments on different outcomes, but only two significant total effects: an improvement of health after melatonin treatment, and a reduction in behaviour problems after light therapy. Surprisingly, we found no evidence to support the hypothesis that these effects were caused by sleep improvement, rather they appeared to be direct effects of the treatments.

The direct effect of melatonin on health is supported by research showing that melatonin has antioxidant properties^{13,14} and beneficial effects on the immune system.¹⁵ The findings from Chapter 3 and Chapter 7 seem contradictory, but the results are not directly comparable. In Chapter 3 we looked at

post-treatment correlations between total sleep time and health, for melatonin treatment only, whereas in Chapter 7 we looked at the effects of the change in sleep from baseline to treatment on the change in health for the total group of children (placebo, light and melatonin).

The reduction in behaviour problems after melatonin treatment described in Chapters 2 and 4, was not apparent in the RCT results reported in Chapter 7 either, but this discrepancy can possibly also be attributed to the differences in the design and statistical analyses of the two studies.

RECOMMENDATIONS FOR FUTURE RESEARCH

The results from the studies described in this thesis seem to suggest that melatonin treatment should be continued for a longer period of time. However, following this suggestion would ignore the concerns and criticisms that are raised against (long term) use of melatonin, concerning possible effects of melatonin on pubertal development and reproductive function.¹⁶⁻¹⁸ In this respect it is important to mention that concerns about possible effects are largely based on animal studies,^{17,18} and that effects on humans appear much less significant.¹⁹ In addition, several studies have been conducted in which no harmful effects of long term melatonin use were found.²⁰⁻²² However, these studies have been criticised as well for having no endocrine assessments, and for shortcomings related to study samples and design.¹⁸ Therefore, more research is needed into the long-term effects of melatonin treatment.

Until the safety of long-term melatonin use has been definitely established, it is important to keep searching for an alternative, also considering the fact that it is not desirable in itself that children are dependent on taking melatonin tablets for a longer time. Short term melatonin treatment was found to lead to loss of effects (Chapter 2), also when applying classical conditioning (Chapter 4). However, future research could focus on establishing optimal treatment duration. In addition, as our results suggest that there might be some effects of classical conditioning in preserving treatment effects (Chapter 4), other protocols of classical conditioning should be investigated, with other stimuli applied only at bedtime, with larger samples with and without comorbidity.

Light therapy also has effects on sleep onset problems, but effects were smaller than those of melatonin (Chapter 6). This does not mean light therapy should be abandoned as treatment for sleep onset problems in children, as our light

protocol had some limitations. We did not shift the timing of bright light use, as is generally recommended,^{12,23} because this might decrease feasibility and thereby treatment adherence. Furthermore, it would be advisable to limit light exposure in the evening, for instance by having children wear dark glasses, and to measure light exposure with light meters, in order to be able to control for light exposure during the day. In addition, attention should be paid to possible side effects of light therapy, such as possible retinal damage through light emitting diodes.^{24,25} For future research, it is important to study adapted light therapy protocols, also in combination with melatonin treatment.

Although melatonin and light therapy improved sleep, effects on cognitive, health and psychosocial functioning were much smaller (Chapter 7). It should be noted however, that 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. Therefore, more research should be conducted into the cognitive, health and psychosocial effects of melatonin treatment and light therapy, with larger samples, to contribute to designing optimal treatment for sleep onset problems in children.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Although the results of our studies suggest melatonin is the preferred treatment in practice, we strongly advise to use melatonin only under proper supervision of an expert medical specialist. A thorough diagnosis should be made and melatonin should only be prescribed for sleep disorders that are related to a disturbance in the biological clock (e.g., DSWPD). In addition, sleep hygiene should be discussed with children and their parents, to see whether the problem might be behaviourally induced and treated.

For sleep disorders that are real circadian rhythm disorders, behavioural solutions will probably not suffice. However, the distinction between circadian rhythm disorders and other sleep disorders is not always strict, as patients with DSWPD may also develop an insomnia when trying to fall asleep at an inappropriate time according to their biological clock,²⁶ and a clear definition of DSWPD in children is lacking. It is therefore important to always discuss sleep hygiene with children and their parents, and to obtain a clear picture of the type of sleep problems experienced by children, so that the most suitable treatment can be advised.

If proper sleep hygiene is applied but ineffective, and the child does seem to have a biological clock disturbance, as indicated by the anamnesis and prefer-

ably also by DLMO, melatonin use would be indicated. Although melatonin is freely available in several countries, among which the Netherlands, self-support use of melatonin can have no or even reverse effects on sleep problems, if it is taken at the wrong time or in the wrong dose. Dose and timing of melatonin administration are very important for the success of the treatment,²⁷ that is why it is advocated to measure DLMO before the start of treatment, to determine the most appropriate time of administration.²⁸ In addition, one should search for the lowest effective dose in treatment, and consider lowering the dose during treatment to see whether this is still effective (see Chapter 2). Until safety of long term use is established with certainty, it is important to follow the guidelines mentioned above and to carefully pay attention to any adverse effects patients may experience.

Melatonin is found to significantly improve DLMO and various sleep outcomes, but in clinical respect most effects are quite small. In our RCT (Chapter 6), according to actigraphy data, sleep latency decreased with 15 minutes and was still longer than 30 minutes, and total sleep time increased with only 5 minutes. Although subjective effects were larger and most children and parents were very satisfied with the effects of melatonin, which is supported by previous research that found that 87.8% of parents indicated that melatonin was an effective treatment for the sleep problems of their child,²¹ it is worthwhile to look for ways to enlarge melatonin effects.

Some suggestions about how this can be achieved are given by recent treatment guidelines,²⁷ which advise that melatonin should be given 3-5 hours before DLMO. This would mean that melatonin should be administered earlier than 19:00 h, as was the case in our studies. However, this can have a soporific effect and make children already sleepy before the evening.¹ Moreover, the dose could be lowered when the effect disappears during treatment which could result from slow melatonin metabolism, and the lowest effective dose should be determined.²⁷

Although more research into long term effects of melatonin is needed, it is important to realise that not treating serious sleep problems in children effectively, is harmful for their (future) physical and mental health, considering the large amount of evidence into the negative effects of sleep problems. Melatonin treatment is effective in advancing sleep, and can result in a child that feels more rested, healthy, better able to concentrate at school and shows less behaviour problems. Therefore, until an equally effective alternative is found, melatonin might be the designated treatment for children with sleep onset problems related to a disturbance in their circadian rhythm.

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