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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 1

Introduction

CASE ILLUSTRATION

Jorrit is a nine-year-old boy, in the fourth grade of elementary school. He is an active boy with lots of friends, who loves playing football and he does relatively well at school. However, he has never been a very good sleeper. He has always had difficulties falling asleep, and fell asleep at a progressively late time over the years. He is often still awake when his parents go to bed, but when he finally does fall asleep he sleeps quite well. He is usually still fast asleep when his father wakes him up in the morning to go to school, and has much difficulty getting out of bed. Jorrit feels very sleepy in the morning and is often tired during the day. In the weekends, he prefers to go to bed later and sleep until late in the morning, but on Sunday evenings he has much trouble falling asleep earlier.

Jorrit lately has difficulties concentrating and paying attention at school, and he shows some hyperactive behaviour. His teacher at school advised Jorrit's parents to have him tested for ADHD, but his parents feel that his chronic sleep reduction might be the underlying problem. They have tried several things, such as making his room dark, not letting him watch TV or using the computer in the hours before he goes to bed, adhering to a bedtime routine and keeping regular bedtimes, but all without any result. They feel the situation has to change soon as his results at school are getting worse and he increasingly reacts irritated and gets into arguments with his parents and younger brother. However, they do not know what to do anymore. Why can't he just fall asleep at a normal time?

The present thesis aims to answer the questions of Jorrit and his parents. Why can't he fall asleep at a normal time, and what can be done about his sleep problems? In this thesis the effects of two different treatments for chronic sleep onset insomnia in children are discussed. **Chapters 2-4** focus on the effects of discontinuing short-term melatonin treatment. **Chapter 5** gives a systematic overview of the effects of bright light therapy, an alternative to melatonin treatment, on sleep problems. **Chapters 6 and 7** describe the results of a randomised controlled trial, in which the effects of melatonin treatment and light therapy on sleep and cognitive, health and psychosocial outcomes are compared. But first, the importance of sleep for children's development will be discussed.

IMPORTANCE OF SLEEP FOR CHILDREN'S DEVELOPMENT

Sleep is essential for growing children. Not only literally, as growth hormone is released during (deep) sleep,^{1,2} but also because there is ample evidence that sleep is related to various aspects of daytime functioning. Reviews about research in children and adolescents yield strong evidence that sleep quantity and quality are associated with capacity to learn and school performance,^{3,4} and that insufficient sleep is related to worse achievement on tests measuring more complex cognitive functions.^{5,6} Changes in sleep are related to changes in cognitive performance in children over time,⁷ and chronic sleep reduction is related to worse school performance.⁸

Moreover, time in bed and sleep quality are predictive of adolescent's behaviour problems,⁹ and sleepiness, which can be considered a consequence of insufficient or low-quality sleep, is related to more behaviour problems and negative mood.¹⁰ In addition, early and persistent sleep problems in childhood are predictive of later emotional and behavioural difficulties,^{11,12} and research in adolescence shows that chronic insomnia has severe negative consequences for future health.¹³

The importance of sleep for physical health is also apparent from research showing the relation between short sleep duration and an increased risk for overweight and obesity in children.¹⁴⁻²¹ Moreover, short sleep duration in combination with irregular sleep times is associated with adverse metabolic outcomes.²² Apart from the relation between sleep duration and (over)weight, studies in adults have given evidence that both short and long sleep duration forecast cardiovascular outcomes²³ and increased mortality risk.²⁴

SLEEP PROBLEMS IN CHILDREN

Sleep is of vital importance for children's functioning, but good quality sleep is not self-evident. In fact, many children experience sleep problems at a certain period during childhood, although prevalence rates vary much between studies due to differences in definitions, research methods, and type of sleep problems studied. A study using medical records reports that only 3.7 % of children who visited a paediatric practice had a sleep disorder diagnosis, which, as the authors remark, is likely to be an underdiagnosis,²⁵ as studies using parent- or child-report data report prevalences of sleep problems between 20 and 30 %²⁶⁻²⁸ or even higher.^{29,30} Although many of these sleep problems are benign and transient, a substantial number of children experience more persistent problems as is clear from longitudinal research showing that approximately 60% of the children who had difficulties initiating sleep still experienced these difficulties one year later.²⁹

Of the various types of sleep problems, sleep onset problems are one of the most frequently reported.^{28,29} Sleep onset problems in children can develop at an early age and have different causes, such as night-time fears or lack of limit-setting by parents.³¹ In addition, sleep onset problems can be caused and reinforced by inadequate sleep hygiene, such as keeping irregular bedtimes, being very active before going to bed, and watching TV or using the computer before bedtime.³² For a subgroup of children the sleep onset problems are related to a delay in markers of the circadian rhythm, such as Dim Light Melatonin Onset (DLMO), which is indicative of a Delayed Sleep Wake-Phase Disorder (DSWPD).³³

DSWPD is a sleep disorder in which the sleep-wake rhythm is delayed with respect to the day/night cycle. It is characterised by an inability to fall asleep at the desired time and extreme difficulty to wake up on time in the morning.³³ Since the diagnosis of DSWPD is not clearly defined and recognised in children, we use the term 'chronic sleep onset insomnia with late melatonin onset' to describe our study population. These are children who have chronic sleep onset problems, as indicated by complaints of inability to fall asleep at the desired clock time and a latency between lights-off time and sleep onset (sleep onset latency) of more than 30 minutes. In addition, they experience these symptoms for at least 4 nights a week, for at least 1 month during a regular school period, and their sleep problems result in problems with daytime functioning, such as sleepiness and tiredness during the day, concentration problems, and behavioural problems. The problems in daytime functioning are caused by the fact that, despite falling asleep late, these children do have to get up on time to go to school, resulting

in a sleep deficit. Although for some of these children behavioural factors may play a role in the development and maintenance of the sleep problems, for many of these children the sleep problems have developed from a very early age, and the impression is that they may have a genetic cause (e.g., they could be related to a Per3 polymorphism).³⁴

As the diagnosis of DSWPD is not much applied in children, little is known about the prevalence. However, research in adolescence reports prevalences of 6-8%,^{35,36} and research in adults with circadian rhythm sleep disorders show that more than 60% of the patients report that their sleep problems started in early childhood.³⁷ Together with the negative consequences of sleep disorders in children, this emphasises the importance of early treatment of childhood sleep problems.

TREATMENT OF SLEEP PROBLEMS IN CHILDREN

There are many behavioural treatment strategies for sleep problems in children. Sleep hygiene and parent education are always important to consider when dealing with sleep problems in children. In addition, behavioural techniques such as various forms of extinction or fading can be used, dependent on the exact type of sleep problems present.³⁸⁻⁴⁰ However, in some cases these behavioural treatment strategies do not suffice, such as in children whose sleep problems are related to disturbances in the circadian rhythm.

CIRCADIAN RHYTHM

The circadian rhythm is one of the two processes regulating sleep as described in the two-process model (originally described by Borbély,⁴¹ but see also Borbély et al.⁴²). According to this model, the circadian process and the homeostatic process regulate the timing of sleep and wakefulness. The circadian process determines periods during the 24-hour period during which the tendency to fall asleep is largest. The homeostatic process describes that sleep pressure increases the longer a person is awake. Circadian rhythms, among which the circadian rhythm of sleep, are orchestrated by the suprachiasmatic nucleus (SCN), located in the hypothalamus.⁴² An important marker of the circadian rhythm is melatonin, a hormone that is induced in the pineal gland and increases sleep propensity. Melatonin secretion increases soon after the onset of darkness with a peak in the middle of the night, and then declines.⁴³ However, when the circadian rhythm becomes

disturbed, e.g., when melatonin secretion is delayed, this can result in sleep problems such as DSWPD, or chronic sleep onset insomnia with late melatonin onset.

MELATONIN TREATMENT

An effective treatment for sleep onset problems related to late melatonin onset is exogenous melatonin treatment. Several studies, among which different randomised controlled trials (RCT), reviews and meta-analyses, found that melatonin is effective in advancing melatonin onset and sleep in children with chronic sleep onset problems.⁴⁴⁻⁴⁹ Moreover, melatonin is also found to be effective for sleep problems in children from special populations, such as children with ADHD,^{50,51} autism spectrum disorders,⁵²⁻⁵⁵ epilepsy⁵⁶ and (other) neurodevelopmental disorders.⁵⁷⁻⁵⁹ However, effects in some studies were small and for some subgroups more RCT's and high-quality studies are recommended in order to be able to draw more firm conclusions.⁵²⁻⁵⁴ Apart from the effects on the melatonin rhythm and sleep, there are some indications of additional effects of melatonin treatment on health,⁴⁷ daytime functioning,⁵⁴ behaviour problems and parenting stress,⁵³ although not all studies found such effects.^{51,58}

Despite the beneficial effects of melatonin summarised above, the use of melatonin has also raised some criticism. To some extent, this criticism is directed towards the uncontrolled use of melatonin, due to its over-the-counter availability in some countries, including the Netherlands. Uncontrolled use of melatonin, without determining the appropriate dose and timing for an individual, can lead to no or even negative effects.⁶⁰ Another part of the criticism is directed towards the lack of rigorous studies investigating the safety of long-term melatonin use.^{61,62} Based on results of animal research, melatonin could have an influence on puberty development and reproductive function.⁶¹⁻⁶³ However, studies that investigated possible negative effects of long-term melatonin use in children did not find any effects,⁶⁴⁻⁶⁶ although these studies have also been criticised for not performing endocrine assessments and shortcomings related to the study samples and design.⁶²

Although studies investigating long-term melatonin use did not find any harmful effects, short term treatment is still preferable over long term treatment, to prevent children from being dependent on taking melatonin tablets for a long time period. Whereas the beneficial effects of melatonin on sleep are clearly

established, the optimal treatment duration is still unknown, and it is not clear if melatonin effects are preserved after discontinuing short term treatment. In addition, not much is known about the effects of melatonin on health and behaviour, and possible effects of improvement of sleep on parenting. Research has shown that parenting is related to sleep problems in children,⁶⁷ and that sleep problems in children might affect parental sleep and subsequently parental mood and parenting.⁶⁸

Therefore, we studied the consequences of gradual termination of short term melatonin treatment in children with delayed Dim Light Melatonin Onset on sleep, health, behaviour problems, and parenting stress (Chapter 2), and also when applying classical conditioning (Chapter 4). Chapter 3 discusses the additional effects of melatonin on health, child behaviour and parenting stress and underlying mechanisms, by examining whether these effects are dependent on the direct effects of melatonin on sleep.

BRIGHT LIGHT THERAPY

As the first three chapters show that it is not possible to discontinue melatonin treatment after a short period without disappearance of the beneficial effects of melatonin, we investigated an alternative treatment for this type of sleep problems: bright light therapy. Light is an important 'zeitgeber' for the circadian rhythm, as it informs the SCN about day length through the eye and the retino-hypothalamic tract. In addition, bright light suppresses the secretion of melatonin, and thereby hampers sleep onset. Light also influences the sleep-wake rhythm through its alerting effects.^{69,70}

Since researchers in the 1980s showed that the circadian rhythm could indeed be influenced by means of light^{71,72} and that light could be used to treat sleep problems,⁷³ several studies have investigated the effects of bright light therapy on sleep. However, these studies have yielded inconsistent results, as some studies found positive effects whereas others found minor or even no effects.⁷⁴⁻⁷⁷ An overview of the effects of light therapy on sleep problems is currently lacking. Therefore, we conducted a meta-analysis to provide a systematic overview of the effects of light therapy on sleep problems (Chapter 5).

Apart from the use of light therapy in the treatment of sleep disorders, there is also evidence of effects of light therapy on other outcomes, such as mood and depressive disorders.⁷⁸⁻⁸⁰ However, these findings are based on studies conducted

in adult populations, as light therapy has not been investigated in children. In order to investigate whether bright light therapy could be an alternative to (long term) melatonin treatment for chronic sleep onset insomnia in children, we conducted an RCT in which we compared the effects of melatonin treatment and light therapy on sleep. The results are summarised in Chapter 6. Chapter 7 describes the cognitive, health and psychosocial outcomes of the RCT. In the latter, we also examined whether melatonin and light therapy had direct effects on these outcomes, or whether effects were mediated by sleep.

OUTLINE OF THIS THESIS

In sum, there is quite some evidence for positive effects of melatonin treatment on chronic sleep onset problems in children. However, especially in young children, short term treatment is favourable over long term treatment.

In this thesis, we look for alternatives to long term melatonin use, by answering the following research questions: What are the effects of discontinuing short term melatonin treatment for chronic sleep onset insomnia in children? Does classical conditioning help to preserve effects? Is light therapy a good alternative to melatonin treatment? What are the effects of light therapy on sleep and cognitive, health and psychosocial outcomes, compared to the effects of melatonin? And can effects of the treatments on cognitive, health and psychosocial outcomes primary be attributed to sleep improvement, or to the treatments themselves?

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