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Delayed sleep phase syndrome and melatonin treatment: A meta-analysis

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Forord

Idéen til dette prosjektet kommer fra veileder, Oddgeir Friborg. I fellesskap ble vi enige om tema, vurderte problemstillinger og hvordan arbeidet skulle utføres. Gjennom prossessen har forfatter hatt mye ansvar og har utført store deler av arbeidet, med tett oppfølging underveis. Derfor ønsker jeg å takke min veileder for stor tålmodighet, engasjement, uvurderlig hjelp og konstruktive tilbakemeldinger, samt hans tilgjengelighet gjennom hele prossessen. Takk for all kunnskap du har delt og alt du har lært meg. Videre vil jeg gi en stor takk masterkoordinator, Tove I. Dahl, for at hun har bidratt med motivasjon og positivitet, og Institutt for psykologi, for mine fem flotte år som student hos dere. En stor takk til mine medstudenter for godt sosialt miljø, støtte og innspill, fra tips til artikler til problemer med data. Og til slutt en stor takk til mamma, pappa og Kjell for gode ord og forståelse på veien.

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Carina Femoen Engebråten

Oddgeir Friborg

Abstract

Delayed sleep phase syndrome is a sleep disorder occurring among children and adolescents, creating difficulty with functioning normally during daytime as sleep-wake cycle is displaced. The diagnosis is common, but there are no standardized treatment guidelines. Research in recent years has found the hormone melatonin to have effect on sleep and shifting the sleep-wake cycle in humans. This meta-analysis aims to identify the effects of melatonin on delayed sleep phase syndrome. A systematic literature search was conducted in PsychINFO, Web of Science, PubMed and Medline from 4. October 2013 to 26. March 2014. Total of eleven studies containing 486 participants were included in the meta-analysis. Five essential sleep parameters were analyzed with the computer program "Comprehensive Meta - Analysis Version 2". The results demonstrated moderate to strong effects, indicating that intervention with melatonin has an enhancing effect on patients with delayed sleep phase syndrome.

Key words: melatonin, delayed sleep phase syndrome, meta-analysis

Sammendrag

Delayed sleep phase syndrome er en søvnforstyrrelse som oppstår blant barn og unge voksne, som forårsaker vanskeligheter med å fungere normalt på dagtid når søvn-våken rytmen er forskjøvet. Diagnosen er vanlig, men det er allikevel ingen standardiserte rettningslinjer for behandling. Forskning de siste årene har funnet ut at hormonet melatonin påvirker søvn og endring av søvn-våken syklusen hos mennesker. Denne meta-analysen har som formål å identifisere effektene av melatonin på DSPS. Et systematisk litteratursøk ble foretatt i PsychINFO, Web of Science, PubMed og Medline fra 4.oktober 2013 til 26. mars 2014. Totalt ble elleve studier med tilsammen 486 delatakere inkludert i meta-analysen. Fem essensielle søvn parametre ble analysert med dataprogrammet "Comprehensive Meta-Analysis Version 2". Resultatene viste moderat til sterk effekt som indikerte at melatonin har en forbedrende effekt på pasienter med DSPS.

Stikkkord: melatonin, delayed sleep phase syndrome, meta-analysis

Contents

Delayed sleep phase syndrome and melatonin treatment: A meta-analysis

Humans and animals alternate between wakefulness and sleep state in a cyclic manner corresponding to the environment with respect to daylight, access to food and varying temperature. The environment follows a 24-hr cycle, and timing of sleep is biologically adapted to follow this clock. The biological endogenous rhythm is however a bit longer than 24-hr (approximately 12-15 minutes) (Wyatt, Ritz-De Cecco, Czeisler, & Dijk, 1999). Hence a mismatch between the environmental and the circadian rhythm will develop unless the circadian clock is rest or advanced each day to stay synchronized with the daily spin of earth.

Sleep and waking is controlled by intrinsic brain mechanisms which was first described in a model of Borbely (1989), also known as the two-process model of sleep and sleep regulation. The model states that the circadian system is regulated by an interaction between two processes: an endogenous biological process (the circadian factor) and a homeostatic factor (Bjorvatn & Pallesen, 2009; Borbely, Achermann, Trachsel, & Tobler, 1989). This model addresses the anatomical and cellular components of the sleep system, explaining how the features of both homeostatic process and the circadian rhythm interact and regulates the onset and amount of sleep (Carskadon, Acebo, & Jenni, 2004).

Sleep regulation

Increasing sleep research the recent years has increased our understanding of the mechanisms underlying the regulation of circadian sleep rhythms and its role for human sleep-wake functions. This insight has shown that several factors interact and that no single mechanism operates alone (Dijk & Lockley, 2002).

Circadian rhythms. Through evolution, the circadian rhythm has caused an adaptive behavior in both humans and animals related to avoidance of predators and access to food during night. However, in animals adapted for nocturnal (night-time) activity, an inverse

relation is present as it is more beneficial. Regardless, humans are adapted for diurnal (day-time) activity, as this is more beneficial (Aschoff, 1965). A range of circadian rhythms beyond the regulation of sleep is also important, such as body temperature, hormone secretion and gene transcription (Refinetti & Menaker, 1992; Wirz-Justice, 2003).

The circadian rhythm is governed by the suprachiasmatic nucleus (SCN), also called the body's master circadian clock (Chesson, Littner, Davila, Anderson, Grigg-Damberger, Hartse, Johnson, & Wise, 1999; Reid & Zee, 2011). SCN is a small region of the brain located in the anterior hypothalamus, above the optic nerves, composed of several types of single-cell circadian oscillators responsive to light stimuli. Retina keeps the human body constantly updated on the level of ambient light. When light hits the ganglion cells in retina, signals are sent to the SCN and neurons are firing (Skene, 2003). When constant reporting about brightness and darkness, it coordinates our endogenous circadian rhythm with respect to daylight (Reppert & Weaver, 2001; Saper, Scammell, & Lu, 2005).

SCN is synchronized by the light-dark cycle which regulates the pineal gland, a small endocrine gland located in the vertebrate brain. The pineal gland secrets a substance called melatonin, also known as the body's sleep hormone (Brzezinski, Vangel, Wurtman, Norrie, Zhdanova, Ben-Shushan, & Ford, 2005; Dahlitz, Alvarez, Vignau, English, Arendt, & Parkes, 1991). This substance plays a major role in the regulation of the sleep-wake cycle in humans, inducing drowsiness and sleep during the evening when daylight is absent (Chang, Reid, Gourineni, & Zee, 2009; van Geijlswijk, Korzilius, & Smits, 2010).

Endogenous melatonin inhibits the central nervous system and provides a gradual transition from wakefulness to sleep. The hormone is secreted by the receptors in the central nervous system causing physical reactions which make the body relax and feel drowsy. Melatonin levels rises in the evening and the body becomes increasingly tired until sleep occurs, and the level drops in the morning and the body wakes up (Mundey, Benloucif,

Harsanyi, Dubocovich, & Zee, 2005; Shochat, Haimov, & Lavie, 1998). A recent study supports this theory about melatonin inhibition and secretion. Lewy, Emens, Jackman, and Yuhas (2006) examined the effect of bright light (daylight) and secretion of melatonin in humans, and found supportive evidence that light breaks down the separation of melatonin.

The homeostatic process. The term homeostatic sleep refers to the sleep-wake aspect in sleep regulation and to a physiological process which maintains many of the states in organisms. The homeostatic process is a result of the level of brain activity during wakefulness, and is to an extent limited by genes in the individual. This factor is believed to be of main importance for sleep quality, as the longer a person is awake the more sleep pressure will accumulate (Kang & Chen, 2009). Higher sleep pressure also implies deeper sleep, while deep wave sleep exponentially reduces sleep pressure (Fig.1).

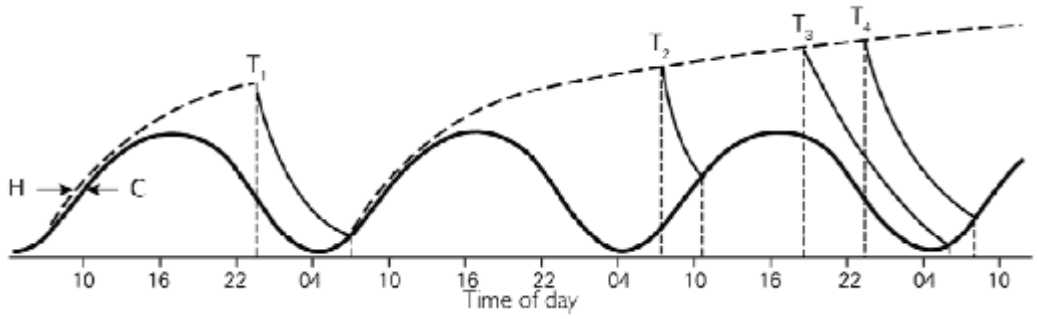

Figure 1. The interaction between homeostatic factor (H) and the circadian factor (C) controls the sleep length. H built up during wake time, and pressure drop during sleep. Waking occurs when H crosses the C curve. Reprinted from Ursin, R. (2008)

Borbély (1982) presented the two-process model which describes how the interaction between the circadian rhythm (Process C) and the homeostatic process (Process S) determines human sleep propensity. The interaction can be confirmed through measurements of brain activity.

EEG is used to examine human brain activity and have shown that slow wave activity, which takes place during deep sleep, is a function of sleep-wakefulness. Brain waves move slower during sleep, while the amplitudes amplify. The homeostatic factor represents a sleep propensity that accumulates during time awake, and reflects the extent of slow-wave activity. After longer periods awake, EEG has shown that there is an increase in slow-wave activity. This observation seems to indicate that Process S gradually increases during the wake episode. Findings from Beersma, Daan, and Dijk (1987) and Dijk, Beersma, and Daan (1987) supports this model and hypothesis. Their experiment concluded that naps late in the day showed increased slow-wave activity.

The interaction between the circadian and the homeostatic processes prove that it is essential to be awake for more than a certain number of hours, considering the slow-wave activity, in order to achieve good quality sleep. It is also important to maintain normal bed and rise times to achieve stable sleep duration (Byberg, Hansen, Christensen, Vistisen, Aandahl, Linneberg, & Witte, 2012). This indicates that it is not possible to obtain a long, deep sleep if going to bed in the biological morning, as the circadian clock then counteracts the homeostatic factor and produce sleepiness the next day.

There are factors which can affect human circadian rhythm. An important impact factor on the sleep-wake cycle is external time-indicating stimuli called zeitgebers (time-givers). These are external cues affecting our body which leads to either awakening or sleep, as for example light exposure, temperature, social interactions and eating/exercise habits, however, light is the strongest. A morning dose of bright light is the most potent zeitgeber for entraining and preventing the circadian clock from free-running (Barion, 2011). But for some individuals the external and the internal mismatch become too large, and a chronic misalignment between endogenous circadian rhythm and the environment occurs, characterized as circadian rhythm sleep disorders (Regestein & Pavlova, 1995).

Delayed sleep phase syndrome

Circadian rhythm sleep disorders exist in varying degrees. Sleep onset, sleep offset, sleep duration, shift the sleep cycle forward or backward, are some of the changes that might affect the circadian rhythm. Any type of sleep disorder creates incomplete sleep and high level fatigue in everyday life (Bjorvatn & Pallesen, 2009). In some cases, when the entire sleep cycle is totally shifted relative to the surroundings can cause individuals to wake up at night and doesn't fall asleep until the morning. When these shifts are considerably and strongly interfered with the ability to function well the next day, a diagnosis of delayed sleep phase syndrome (DSPS) may be indicated. Although, sleep timing may strongly shift in DSPS. The duration of sleep is normally unaffected (approximately 8 hours) if one is allowed to sleep freely, and the quality of sleep is normal (Chang, Reid, Gourineni, & Zee, 2009; Ozaki, Uchiyama, Shirakawa, & Okawa, 1996).

DSPS was suggested as a diagnosis by Weitzman in 1981, which also represent a form of sleep onset insomnia (Weitzman, Czeisler, Coleman, Spielman, Zimmerman, Dement, & Richardson, 1981). The disorder is characterized by a chronic difficulty of falling asleep according to normal bedtimes, for example more than 3-6 hours later than socially acceptable bedtimes. Typically, a sleep onset later than 2 a.m. is a required criterion. For people having social obligations early in the morning (e.g., job, or school), difficulty with functioning normally during daytime is another major complaint. The fact that most people with the disorder are forced to attain school or work early in the morning, might worsen the situation significantly and may lead to chronic sleep problems (Chang et al., 2009; Dagan, Yovel, Hallis, Eisenstein, & Raichik, 1998) (Fig.2).

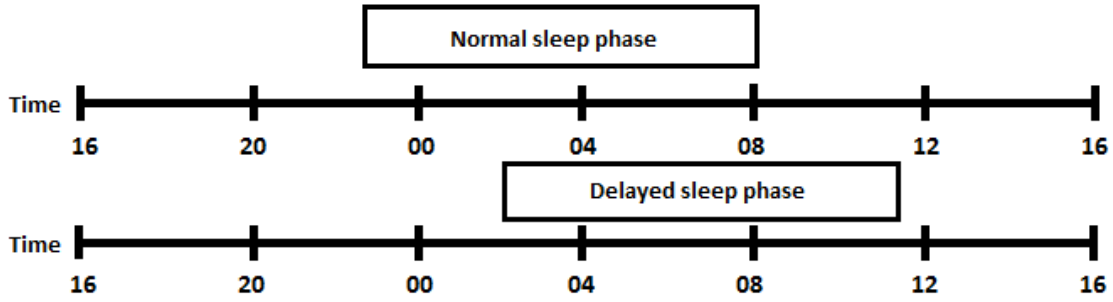

Figure 2: The normal human sleep phase curve where sleep onset is about 10:00 and sleep offset is about 8:00, compared with the delayed sleep phase response curve where sleep onset is about 02:00 and sleep offset is about 11:00. Reprinted from A. Barion, P.C. Zee; Sleep Medicine 2007; (8): 566-577.

DSPS patients suffer from daytime sleepiness, feeling tired in the morning and most alert in the late evening (Reid & Zee, 2011). Suffering from severe drowsiness in the morning and never feeling completely rested, will be an obstacle in many areas. There can be problems following up the social life, work difficulties, poor academic performance and several health issues; mentally and physically, in terms of stress and depression (Cole, Smith, Alcala, Elliott, & Kripke, 2002; Rahman, Kayumov, & Shapiro, 2010).

Prevalence. DSPS is believed to be the most common circadian rhythm sleep disorder, but well-designed prevalence studies are rare (Dagan et al., 1998). DSPS seems to be common among adolescents and young adults, with prevalence between 7-16% (Lack, 1986). A Norwegian study (Schrader, Bovim, & Sand, 1993) assessed a prevalence of 13-17% from an adult sample, whereas a prevalence of 14% was reported from a Japanese study (Yazaki, Shirakawa, Okawa, & Takashi, 1999). These results were measured through questionnaires; therefore results can be inaccurate and limited by the design.

However, evidence indicates that DSPS occurs on the basis of biological mechanisms, because the disorder is represented across races and cultures, and appears to be related more

to puberty than old age (Saxvig, Pallesen, Wilhelmsen-Langeland, Molde, & Bjorvatn, 2012). Suggesting psychosocial factors to affect the displacement of the sleep-wake rhythm are due to pressure from social norms to stay up late in the evenings, combined with a reduction of parental influence about sleep patterns. A displacement of the sleep-wake rhythm may be affected by puberty, where bodily changes lead to drowsiness and increased preference for being awake longer at night (Lack, 1986; LeBlanc, Morehouse, Rajda, Kutcher, Hayden, Thompson, & Rusuk, 1999).

According to two-process model of sleep regulation, which explain sleep regulation through an interaction between the homeostatic process and the circadian process, homeostatic process creates a drive for sleep when the body has been awake for hours, while the circadian process lead to sleep propensity. The processes together appear to cause sleep delay, when delaying the biological clock and slowing down the homeostatic drive, the sleep period is postponed to a later phase of the circadian rhythm (Hagenauer, Perryman, Lee, & Carskadon, 2009).

Treatment. The very first treatment method for DSPS was based on chronotherapy which involves shifting the sleep-wake cycle gradually, by waking up earlier until the desired timing of sleep is achieved (Czeisler, Richardson, Coleman, Zimmerman, Mooreede, Dement, & Weitzman, 1981). The technique works by strictly following and maintains specific bed and wake times every day, but disturbances can quickly occur and the treatment fails (Hizli & Agargun, 2009). Chronotherapy is also time consuming and not a recommended treatment, as some cases has resulted in free running disorder after treatment (Medicine, 2005).

Other approaches of treating DSPS have been shown to work better than chronotherapy. The most common treatment approaches in the recent years is using carefully timed “morning” light administration and “evening” melatonin treatment, which affects the circadian rhythm to shift (Pandi-Perumal, Trakht, Spence, Srinivasan, Dagan, & Cardinali,

2008). To achieve an effective treatment using light and melatonin is it dependent on correct time of administration relative to the circadian clock. Despite the fact that there are studies based on the use of bright light and melatonin, there are varying results and no standardized treatment guidelines exists (van Geijlswijk et al., 2010).

Characteristics describing the cycle of the circadian clock is wake up time and dim light melatonin onset (DLMO). DLMO represents increased melatonin levels in the body, normally two hours before falling asleep if the light is dim, and levels declining hours before awakening. It serves as a marker for circadian phase which can be used to time the administration of bright light or exogenous melatonin in order to elicit a desired phase shift. Melatonin levels and DLMO can be studied through the use of the phase response curve (PRC) that illustrates how the circadian rhythm changes throughout the day. Estimating the DLMO can be done through blood or saliva samples (Burgess, Revell, Molina, & Eastman, 2010).

Exogenous melatonin treatment. Exogenous melatonin functions as a chronobiotic drug with hypnotic properties, shown to shift the internal biologic clock. Several controlled studies addressed the effect of melatonin as treatment on delayed sleep phase syndrome. Szeinberg, Borodkin, and Dagan (2006) examined the effect of melatonin in adolescents diagnosed with DSPS. Patients were treated with 3-5 mg melatonin per day for an average period of six months. The results were significant indicating that melatonin advanced the average sleep onset time with 2 hours, reduced sleepiness and increased sleep duration.

However, the effect of melatonin appears to vary between sleep parameters. Another study (Kayumov, Brown, Jindal, Buttoo, & Shapiro, 2001) examined the effects of melatonin on sleep, daytime sleepiness, fatigue and alertness in patients diagnosed with delayed sleep phase syndrome, and found no effect on sleepiness. Patients took 5 mg melatonin per day, between 19:00 and 22:00, in total eight weeks. The results showed that a high dose of

melatonin significantly reduced sleep onset latency, but there was no significant decrease in total sleep time or subjectively reported improvement of daytime sleepiness, fatigue and alertness.

On the other hand, another study (Mundey et al., 2005) reported different results. In the study, participants received a weak dose of 0.3 mg melatonin per day and a stronger dose of 3.0 mg melatonin per day, administered between 1,5 and 6,5 hours prior to dim light melatonin onset, for four weeks. The results showed that both doses of melatonin affected dim light melatonin onset and advanced the circadian phase. These results is also confirmed by an earlier study (Nagtegaal, Kerkhof, Smits, Swart, & Van der Meer, 1998) which examined the effects of 5 mg melatonin per day, 5 hours prior to dim light melatonin onset, in patients with DSPS. Melatonin significantly advanced dim light melatonin onset by 1,5 hours.

Studies' investigating the effect of melatonin treatment on delayed sleep phase syndrome are using different research design, implementations, dosages and study length, which is resulting in varying findings. There are no standardized guidelines for either dose of melatonin, recommended administration time or length of treatment, which may have influenced the results in each study. Some research designs are more suitable for addressing the research hypotheses and to predict the effect of interventions (Borenstein, Hedges, Higgins, & Rothstein, 2009).

On the basis of the aforementioned reasons and variations between studies, it is interesting to consider the overall effect of melatonin on DSPS. By collecting all usable studies and investigate the combined effect of several sleep parameters, are required to contribute more knowledge in the field and better treatment for delayed sleep phase syndrome.

Research aims

The aim of this present study is to examine how well melatonin is suited for the treatment of DSPS. Previous systematic summarization of the field has yet been done, to the author's best knowledge. The treatment effects of melatonin were examined by locating all available published studies. By combining all studies reporting the effect of melatonin with regard to selected sleep parameters, the overall effect of the hormonal treatment should become clearer. Moreover, this meta-analysis might also indicate which sleep parameters that are most strongly affected by melatonin.

Method

Literature search strategies

The databases Embase, PubMed, PsychINFO, Medline and Web of science were searched for relevant articles concerning the treatment of delayed sleep phase syndrome with bright light and melatonin, published between 1980 and 2013. Following keywords were used: “circadian” AND “phase” AND “delay” AND “disorder” OR “syndrome” AND “treatment” OR “intervention” OR “interventions” OR “therapy”. The search resulted in 1699 articles. By reading the abstract of the articles, relevant studies were included and irrelevant studies were excluded. In addition, eligible articles found by reviewing reference lists of included studies.

Literature search was conducted from 4. October 2013 until 26. March 2014. The various search combinations gave a total of 1699 hits: Web of Science resulted in 402 hits, PubMed resulted in 504 hits, resulted in 363 hits, PsychINFO resulted in 170 hits and Medline resulted in 260 hits. Many of the articles were found repeatedly in different data bases. By reviewing the reference lists, seven relevant studies were found, but no one met the inclusion criteria for the analysis. Update search yielded no relevant studies. Unable to track down useful articles by key authors in the field, no unpublished articles were included in the analysis. The literature search gave 20 potentially relevant studies, in which nine were excluded. Finally, there were 11 studies which met all inclusion criteria for meta-analysis.

Inclusion criteria

The aim of studying intervention with melatonin is to see if key sleep parameters will be affected and displaced in the direction of normal sleep cycle. The criteria set for studies to be included in this analysis are described by the type of studies, subjects, interventions and which outcome measures they report.

Studies. All studies had to involve participants with a diagnosis of delayed sleep phase syndrome, with the purpose of assess improvement in sleep parameters following intervention with melatonin. Both randomized trials and studies based on pre-post design with no control groups were included in the analysis, since there were a limited number of studies in this field. No studies older than 1980 was included.

Subjects. Studies were included if subjects in the experiment were diagnosed with DSPS. Participants were men and women, and there was no minimum age limit for inclusion. Studies examining the effect of melatonin treatment on other diagnostic groups, such as depression or anxiety, were excluded.

Interventions. Studies based on clinical trials, therapy or treatment with the aim to improve sleep was included. Review articles were not included.

Outcome measures

To measure and evaluate the treatment effect of melatonin on delayed sleep phase syndrome, five sleep parameters were selected and analyzed separately. The parameters: 1) dim light melatonin onset (DLMO), 2) sleep onset latency (SOL) 3) sleep onset time, and 4) sleep offset time, 5) total sleep time. These parameters may be considered as the most relevant as it indicates whether an increase in melatonin in plasma takes place at an earlier time, whether less insomnia problems are present and whether relevant changes (or advances) in the sleep cycle has occurred. The final parameter, TST, is less relevant as most patients with DSPS have normal sleep quality and sleep hypnograms (Morgenthaler et al., 2007), if allowed to sleep freely. It was nevertheless included to see whether these patients had social obligations early in their biological morning that the TST parameter might give an indication of.

Sleep parameters

An overview of sleep parameters included and analyzed in the analysis.

Dim light melatonin onset (DLMO) is a tool that makes it possible to analyze the circadian rhythm and sleep in humans. During the course of the circadian rhythm, melatonin is secreted into salvia as a feature of SCN functions. Several studies have proven and concluded that within this rhythm, the onset of melatonin secretion under dim light conditions is the most accurate marker to measure the circadian rhythm and sleep cycle in humans (Pandi-Perumal, Smits, Spence, Srinivasan, Cardinali, Lowe, & Kayumov, 2007). DLMO is useful to identify the optimal time to administrate treatment like bright light and melatonin. DLMO measurements can be collected through salvia and urine samples.

Sleep onset latency (SOL), is a term which deals with the transition from wakefulness to sleep state. The term represents the time between going to bed and falling asleep. SOL is often reported objectively using electrophysiological measures obtained from electroencephalogram (EEG), which is a neurophysiological measurement and recording of the brain's electrical activity (Catero, Atienza, Stickgold, & Hobson, 2002).

In addition, sleep onset, sleep offset and total sleep time is emphasized in the analysis. Sleep onset is defined as the time when falling into REM sleep. Sleep offset is defined as the time it takes to go out of sleep into wakefulness. These concepts can be measured objectively with EEG, or subjectively through sleep logs. Total sleep time is the number of hours in a sleep episode (Auger, Burgess, Dierkhising, Sharma, & Slocumb, 2011).

Coding procedure

Studies were coded into the analysis program according to general information: author, year and publication country, information about the sample, the type of intervention, and statistical values such as standard deviation and mean. In addition, several moderator variables were coded from the studies which may have affected the relationship between

interventions and outcomes. As mentioned, it is chosen to ignore the moderator variables since the analysis includes very few studies. Moderator variables were coded, such as treatment duration days, administration time and study design. However, as the number of available studies was limited, additional moderator variables were not conducted.

Statistical analyzes

Effect sizes can be calculated with "fixed effect analysis" or "random effects analysis". "Fixed effect analysis" assumes the existence of a final effect size across studies, which all represent the same size. Large studies are given more weight than smaller studies. "Random effect analysis" assumes that there is variation between the different sleep objectives, design, number of participants, and each study has different effect sizes, which will be represented in the calculation, resulting in a balanced equilibrium (Hedges & Vevea, 1998). On this basis, the effect size is calculated with the "random-effects analysis" to avoid that one study will weigh more than other studies, because of the sample size and the number of outcomes.

Hedge's *g* is used to measure the effect size, and is set as default in the computer program "Comprehensive Meta-Analysis". Hedge's *g* is considered as better than Cohen's d, because it does not estimate the standardized mean difference skewed. Cohen's d is assumed to overestimate the standardized difference of the means in smaller samples, creating bias. Hedge's *g* use the average difference in each study and divides it on each study's standard deviation, and provides a standardized index which makes all the studies comparable even if they have used different data formats (Borenstein et al., 2009).

Heterogeneity analysis was used to investigate whether variations between individual studies may be due two chance (heterogeneity; studies results from different populations studies), or whether there are genuine differences underlying the results (homogeneity; studies results from the same population of studies). Heterogeneity analysis is to ensure that all studies are similar enough to be included in the meta-analysis, calculated from Cochran’s Q-

statistic and the I^2-statistic (Higgins & Thompson, 2002). When moderator variables are not conducted in this meta-analysis, heterogeneity analysis is less relevant.

Q-statistics are investigating whether there is heterogeneity present, the p-value indicates whether it is significant or not, and the I-squared describes the percentage of the total variance in the studies due to heterogeneity. It is suggested that a Q value of 25 is low heterogeneity, value of 50 is moderate, while a value above 75 indicates high heterogeneity. Q-statistic are used to examine variation between the studies and groups, the placebo group and intervention group. If it is significant, the null hypothesis is rejected and it is assumed that there is variation between groups (Borenstein et al., 2009).

The confidence interval conveys the result precision. The plot shows whether the effect sizes are similar from study to study, and whether the effect size of a 95% confidence interval overlaps. A negative effect size indicates a negative outcome of intervention with melatonin, and a positive effect size indicated a positive outcome of the intervention (Turlik, 2009). It was expected that the results from the analysis would demonstrate a positive effect of the intervention, as the analysis highlights positive improvement of DSPS through the use of melatonin as treatment.

Publication bias

“Funnel plot" is a scatter chart that can be used to assess whether the studies conveys publication bias, which can be read as asymmetry in the plot. However, studies are symmetrically distributed with the largest studies placed the chart's top and around the average effect size, and the smaller studies to chart’s bottom, this indicates that there is no publication bias. This plot should be used only if there are 10 or more studies in the analysis, when few studies will not have enough strength to separate the actual asymmetry of coincidences. The plot can indicate whether the absence or presence of unpublished studies.

By using the "trim and fill algorithm", it’s possible to estimate existing studies which is missing from the analysis. This algorithm makes investigates whether significant changes occur in the effect size if unpublished studies are included. "Orwin fail-safe N" is a statistical procedure that can be used to estimate how many unpublished studies did not report any treatment effect, which is needed to make the analysis nonsignificant (Rothstein, Sutton, & Borenstein, 2005).

Results

Study characteristics of included studies

Eleven studies were included in the analysis with a total of 486 participants. All studies were published between 1991 and 2009. Three studies from Canada (Kayumov et al., 2001; Rahman et al., 2010; Wasdell, Jan, Bomben, Freeman, Rietveld, Tai, Hamilton, & Weiss, 2008)., five studies from Holland (Nagtegaal et al., 1998; Smits, Nagtegaal, van der Heijden, Coenen, & Kerkhof, 2001; Smits, van Stel, van der Heijden, Meijer, Coenen, & Kerkhof, 2003; van der Heijden, Smits, van Someren, & Boudewijn Gunning, 2005; van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007), one study from the UK (Dahlitz et al., 1991), and two studies from the USA (Mundey et al., 2005; Oldani, Ferini-Strambi, Zucconi, Stankov, Fraschini, & Smirne, 1994).

Kayumov et al. (2001) included 15 men (age = 35.6 ± 14.0) and 7 females (age = 30.8 ± 12.4), Mundey et al. (2005) included 8 men and 5 women (mean age = 28.15 ± 5.74), Dahlitz et al. (1991) included 8 men (mean age = 34.63), Nagtegaal et al. (1998) included 14 men and 16 women (mean age = 37.3 ± 15.3), Wasdell et al. (2008) included 31 men and 19 women (mean age at baseline = 7.38), Smits et al. (2001) included 28 men and 12 women (mean age in intervention group = 10.3 ± 1.6, mean age in the placebo group = 9.3 ± 1.5), Smits et al. (2003) included 49 men and 13 women (mean age in intervention group = 9.2 ± 2.1, the average age in the placebo group = 10.0 ± 1.7), van der Heijden et al.(2007) did not specify how many of each gender who participated but were aged between 6-12 years, (van der Heijden, Smits, van Someren, and Boudewijn Gunnin (2005) did not specify how many of each sex participating but age was between 6-12 years, Rahman et al. (2010) included 13 men (age = 35.6 ± 14.0) and 7 females (age = 30.8 ± 12.4), Oldani et al. (1994) included 6 participants.

Subjects were recruited through referrals from doctors at sleep clinic/centre (Dahlitz et al., 1991; Oldani et al., 1994; Rahman et al., 2010; Smits et al., 2001; Smits et al., 2003; van der Heijden et al., 2005), referrals from local physicians and psychologists at from polyclinics and institutions (Kayumov et al., 2001; Mundey et al., 2005; Smits et al., 2001; Smits et al., 2003; van der Heijden et al., 2005; van der Heijden et al., 2007; Wasdell et al., 2008), and some recruited additionally through advertisements in newspapers, flyers or television (Kayumov et al., 2001; Mundey et al., 2005).

Effect measurements. The studies varied based on which sleep parameters they reported. Sleep measurements used in the analysis of the included studies are presented in table 1. Some of the studies also reported follow-up data, but this is not included in the meta-analysis.

Design. Nine of the included studies were randomized controlled trials (Dahlitz et al., 1991; Kayumov et al., 2001; Mundey et al., 2005; Rahman et al., 2010; Smits et al., 2001; Smits et al., 2003; van der Heijden et al., 2005; van der Heijden et al., 2007; Wasdell et al., 2008) and two studies were double-blind placebo-controlled cross-over studies (Nagtegaal et al., 1998; Oldani et al., 1994). Two of the studies did not have any control or comparison group, which is thus only assessed treatment effect in the intervention group (Nagtegaal et al., 1998; Oldani et al., 1994).

Intervension. The interventions comprised mainly administration of melatonin pills at specific times, conducted through health professionals, instructed caregivers and participants. Four studies included treatment of participants through caregivers (Smits et al., 2001; Smits et al., 2003; van der Heijden et al., 2005; Wasdell et al., 2008). Two studies focused treatment through health professionals (Dahlitz et al., 1991; Kayumov et al., 2001), while three studies included treatment by healthcare professionals, caregivers and participants (Nagtegaal et al., 1998; Oldani et al., 1994; Rahman et al., 2010; van der Heijden et al., 2007). All studies

involved parts of the intervention carried out by health personnel in advance, afterwards, or both.

Treatment duration. The length of the treatments ranged from 21 days (van der Heijden et al., 2007) to 42 days (Nagtegaal et al., 1998), where a total of nine studies had an intervention length of 27-30 days, and two studies had an intervention length about 21-24 days. The duration of the studies varied according to the number of trials and measurements. The longest study began with measurements of melatonin and body temperature, then six weeks of switching between melatonin and placebo, and ends with the final measurements of the intervention effect (Nagtegaal et al., 1998). The studies with a duration of one month, measured baseline one week before the intervention, with four weeks of melatonin administration ending with measurements of the intervention's effect on sleep (Dahlitz et al., 1991; Kayumov et al., 2001; Mundey et al., 2005; Oldani et al., 1994; Rahman et al., 2010; Smits et al., 2001; Smits et al., 2003; van der Heijden et al., 2005; van der Heijden et al., 2007). One study involved a week with polysomnograph, ten days with melatonin / placebo treatment, three to five days of wash-out, and further ten days with melatonin / placebo treatment. All data were collected on the basis of what caregivers reported (Wasdell et al., 2008).

Reporting. There were a total of five studies that made use of self-report through sleep logs to collect data from participants' sleep hygiene (Dahlitz et al., 1991; Kayumov et al., 2001; Mundey et al., 2005; Nagtegaal et al., 1998; Oldani et al., 1994; Rahman et al., 2010). Five studies used participants' caregivers to report by using sleep log (Smits et al., 2001; Smits et al., 2003; van der Heijden et al., 2005; van der Heijden et al., 2007; Wasdell et al., 2008). Several studies used healthcare providers to collect data from other measurements, such as EEG, urine samples and blood samples.

Table 1

Studies and sleep measurements		Hedges' *g*	95% CI	*p*-value
Kayumov (2001)				
	Placebo: SOL	-0,54	-1,04 to -0,06	.02*
	Placebo: TST	-0,77	-1,31 to -0,30	.00*
	Intervention	0,37	-0,07 to 0,84	.10
	Intervention	-0,5	-0,99 to -0,05	.03*
Mundey (2005)				
	Placebo: DLMO	-0,11	-1,33 to 0,95	.75
	Placebo: SOL	0,08	-1,00 to 1,27	.82
	Placebo: TST	0,4	-0,56 to 1,97	.28
	Placebo: Sleep onset	0,1	-0,96 to 1,32	.76
	Placebo: Sleep offset	-0,17	-1,46 to 0,52	.61
	Intervention: DLMO	0,86	0,13 to 1,80	.02*
	Intervention: SOL	0,24	-0,44 to 0,98	.45
	Intervention: TST	-0,47	-1,27 to 0,21	.16
	Intervention: Sleep onset	0,27	-0,40 to 1,02	.39
	Intervention: Sleep offset	0,46	-0,22 to 1,25	.17
Dahlitz (1991)				
	Placebo: TST	-0,46	-1,25 to 0,23	.17
	Intervention: TST	-1,18	-2,27 to -0,37	.01*
Nagtegaal (1998)				
	Intervention: DLMO	0,78	0,35 to 1,25	.00*
Wasdell (2007)				
	Placebo: SOL	0,21	-0,07 to 0,49	.14
	Placebo: TST	-0,07	-0,35 to 0,21	.62
	Intervention: SOL	0,74	0,44 to 1,06	.00*
	Intervention: TST	0,19	-0,09 to 0,47	.18
Oldani (1994)				
	Intervention: SOL	0,19	-0,53 to 0,97	.57
	Intervention: TST	-0,04	-0,79 to 0,70	.91
	Intervention: Sleep onset	1,59	0,62 to 3,04	.00*
	Intervention: Sleep offset	1,44	0,52 to 2,80	.00*
Smits (2001)				
	Placebo: DLMO	-0,48	-1,01 to -0,00	.05*
	Placebo: Sleep onset	-0,45	-0,98 to 0,02	.06
	Intervention: DLMO	-0,21	-0,86 to 0,40	.47
	Intervention: Sleep onset	0,73	0,08 to 1,51	.03*
Smits (2003)				
	Placebo: DLMO	0,04	-0,31 to 0,40	.81
	Intervention: DLMO	1,63	1,04 to 2,34	.00*
van der Heijden (2007)				
	Placebo: DLMO	-0,21	-0,55 to 0,11	.20
	Placebo: SOL	-0,11	-0,43 to 0,20	.48
	Placebo: TST	-0,28	-0,61 to 0,04	.08

Table 1 (continued)

Studies and sleep measurements	Hedges' *g*	95% CI	*p*-value
Placebo: Sleep onset	-0,21	-0,53 to 0,10	.18
Intervention: DLMO	0,71	0,36 to 1,09	.48
Intervention: SOL	0,76	0,43 to 1,13	.00*
Intervention: TST	0,37	0,06 to 0,70	.02*
Intervention: Sleep onset	0,45	0,14 to 0,78	.00*
van der Heijden (2005)			
Placebo: DLMO	-0,25	-0,57 to 0,06	.12
Placebo: SOL	0	-0,34 to 0,34	.00*
Placebo: Sleep onset	-0,05	-0,39 to 0,28	.75
Intervention: DLMO	0,97	0,57 to 1,42	.00*
Intervention: SOL	0,52	0,16 to 0,90	.00*
Intervention: Sleep onset	0,03	-0,29 to 0,36	.84
Rahman (2009)			
Placebo: SOL	-1,49	-2,46 to -0,75	.00*
Placebo: TST	-10,45	-15,77 to -6,71	.00*
Intervention: SOL	1,28	0,59 to 2,16	.00*
Intervention: TST	-6,63	-10,03 to -4,22	.00*

*p < .05

Intervention effects

Interpreting Hedge's *g*, effect sizes under 0.20 is considered as weak, around 0.50 as moderate, and above 0.80 as strong.

Analysis 1) changes in the dim light melatonin onset (DLMO) after intervention. A total of six studies (133 participants) in the intervention group, whereas a total of five studies (125 participants) in the placebo group were included, totaling 258 participants in this analysis. DLMO after intervention revealed a great significant effect of 0.77 ($p < 0.00$, 95% CI = 0.577 to 0.968), whereas in the placebo group effect was -0.19 ($p > 0.03$, 95% CI = -0.359 to -0.020), which is significantly different from the intervention group. It was found a low and significant heterogeneity in the intervention group (Q = 19.45, df (Q) = 5, $p < 0.00$, $I^2 = 74.29$) between the studies. In placebo group the heterogeneity was low and not significant (Q = 3.373, df (Q) = 4, $p > 0.03$, $I^2 = 0.00$) between the studies.

Analysis 2) changes in sleep onset latency (SOL) after intervention. A total of seven studies (170 participants) in the intervention group, whereas a total of six studies (157 participants) in the placebo group were included, totaling 327 participants in this analysis. SOL after the intervention showed a moderately strong effect of 0.61 ($p < 0.00$, CI 95% = 0,449 to 0,771). The placebo group the effect was -0.08 ($p > 0.32$, CI 95% = -0.234 to 0.077), which was significantly different from the intervention group. There is a low and not significant heterogeneity in the intervention group (Q = 8.93, df (Q) = 6, $p > 0.17$, $I^2 = 32$ 820) in effect between studies. In the placebo group the heterogeneity is low and significant (Q = 20.773, df (Q) = 5, $p < 0.00$, $I^2 = 75.931$) between groups.

Analysis 3) changes in sleep onset time after intervention. A total of five studies (102 participants) in the intervention group, whereas a total of four studies (94 participants) in the placebo group were included, totaling 196 participants in this analysis. Sleep onset time after the intervention showed a weak and significant effect of 0.34 ($p < 0.00$, CI 95% = 0.142 to 0.538). The placebo group effect was -0.17 ($p > 0.09$, CI 95% = -0.361 to 0.027), which was significant different from the intervention group. In the intervention group, there was a low and not significant heterogeneity (Q = 10.835, df (Q) = 4, $p > 0.03$, $I^2 = 63,083$) effect between studies. In the placebo group the heterogeneity was low and not significant (Q = 2.606, df (Q) = 3, $p > 0.46$, $I^2 = 0.00$) between groups.

Analysis 4) changes in sleep offset time between after intervention. A total of two studies (15 participants) in the intervention group, whereas a total of one study (3 participants) in the placebo group were included, totaling 18 participants in this analysis. Sleep offset time after the intervention showed a great and significant effect of 0.76 ($p < 0.00$, CI 95% = 0.208 to 1.302), which was significant different from the placebo group effect of -0.17 ($p > 0.61$, CI 95% = -0.836 to 0.487). Heterogeneity effect in the intervention group is low and not significant between the studies (Q = 2.644, df (Q) = 1, $p = 0.10$, $I^2 = 62,172$). In the placebo

group the heterogeneity was nonexistent (Q = 0.00, df (Q) = 0, $p < 1.00$, $I^2 = 0.00$) between groups.

Analysis 5) changes in total sleep time after intervention. A total of seven studies (146 participants) in the intervention group, whereas a total of six studies (132 participants) in the placebo group were included, totaling 278 participants in this analysis. Total sleep time after the intervention showed an effect of 0.00 ($p > 0.963$, CI 95% = -0.166 two 0.174). The placebo group resulted in a weak effect of -0.25 ($p < 0.00$, CI 95% = -0.424 to -0.071) This indicates that there was no effect on the total sleep length after intervention, but the placebo group showed a significant reduction in total sleep time. It is a moderate and significant heterogeneity effect in the intervention group (Q = 44.587, df (Q) = 6, $p > 0.00$, $I^2 = 86\ 543$) between the studies. In the placebo group the heterogeneity was moderate and significant (Q = 32.153, df (Q) = 5, $p < 0.00$, $I^2 = 84.449$) between groups.

It was generally reported high heterogeneity in the analysis, which is not surprising. There are few studies included in the analyzes which indicate that heterogeneity analysis is somewhat flawed. Based on the small number of studies, it is decided that either heterogeneity analyzes or moderator variables are emphasized further in the meta-analysis.

Results of publication bias analyzes

Analysis 1) Funnel plot of the analysis of DLMO was asymmetric with few studies to both left and right of the average. An asymmetric plot suggests that there is a correlation between the treatment effect and the size of the study (Fig.3). Moreover, this can be investigated further with “trim and fill” analysis. “Trim and fill” was used to make an estimate of how many studies are believed to exist but are not included. It was calculated that n = 0, indicating that there are no missing published studies omitted from the analysis. The last statistical calculation was conducted “Orwin's fail-safe N” with "random effects model",

to see whether publication bias affected the overall result. The analysis showed that 39 additional studies with no effect of melatonin treatment are needed to cause the p-value to be statistically non-significant (p> 0.05).

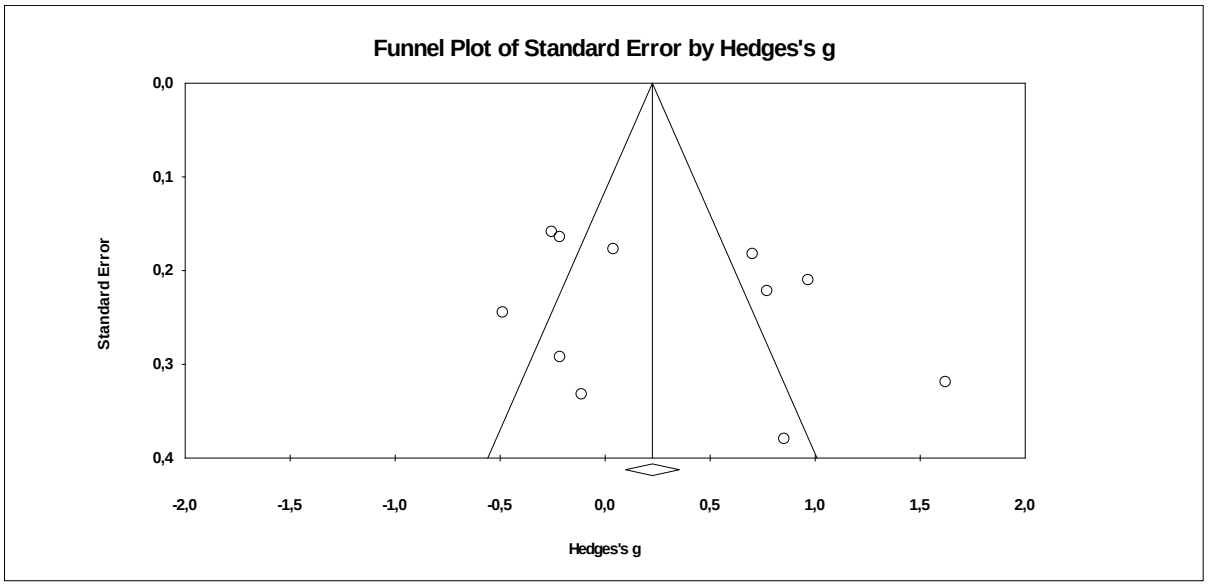

Figure 3. Funnel plot of DLMO analysis

Analysis 2) Funnel plot of the analysis of SOL showed asymmetry with few studies both to the left and the right of the average, which may indicate publication bias, or it might be of lower quality (Fig.4). Furthermore, by measuring how many studies are believed to exist, but not included, the "trim and fill" calculated that n = 1, indicating that there is one missing published study omitted from the analysis. By using "Orwin's fail-safe N" with "random effects model" to assess whether publication bias affected the overall result. The analysis showed that 53 additional studies with no effect of melatonin treatment are needed to cause the p-value to be statistically non-significant (p> 0.05).

ME

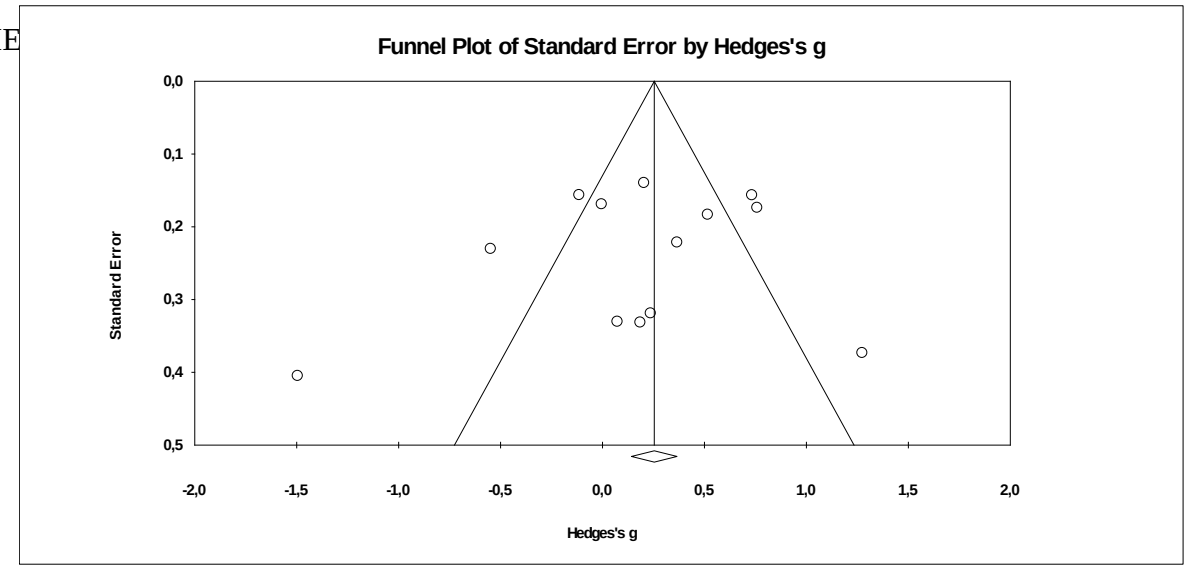

Figure 4. Funnel plot of SOL analysis

Analysis 3) Funnel plot of the analysis of sleep onset time showed asymmetry with few studies placed both sides of the average, including a small study on the right, which may indicate publication bias, or it might be of lower quality (Fig.5). Furthermore, by measuring how many studies are believed to exist, but not included, the "trim and fill" calculated that n = 0, indicating that there are no missing published studies omitted from the analysis. By using "Orwin's fail-safe N" with "random effects model" assessed whether publication bias affected the overall result. The analysis found that six additional studies with no effect of melatonin treatment will cause the p-value to be statistically non-significant (p> 0.05).

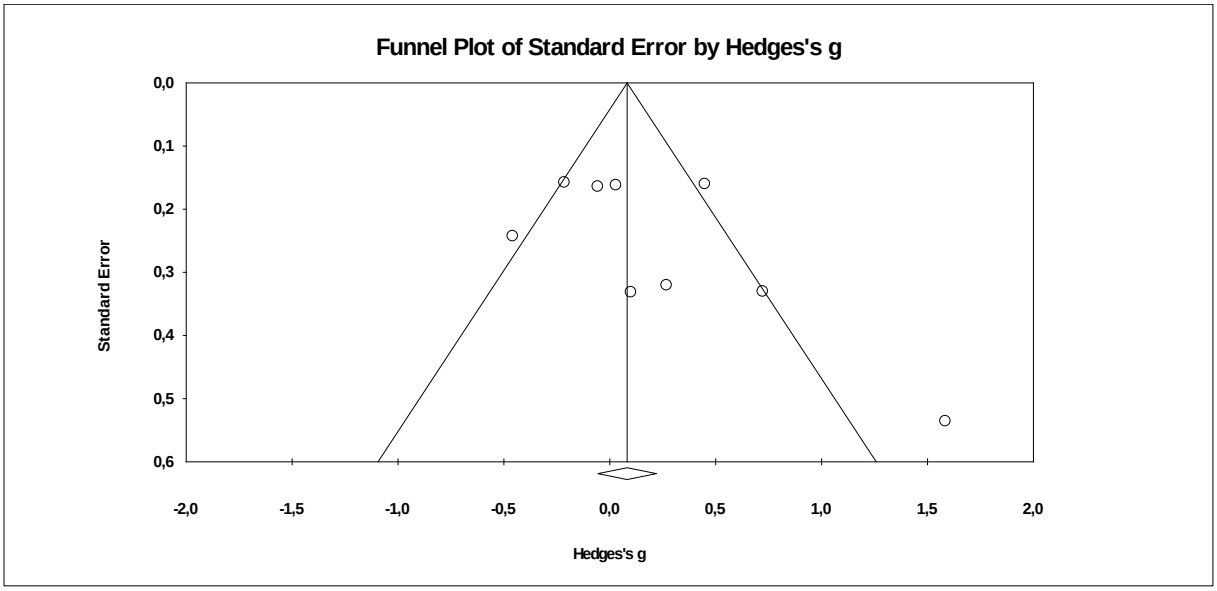

Figure 5. Funnel plot of sleep onset time analysis

Analysis 4) Funnel plot of the analysis of sleep offset time showed a small symmetry with the same number of trials to the left as the right of the average (Fig 6). Furthermore, by measuring how many studies are believed to exist, but not included, the "trim and fill" calculated that n = 0, indicating that there are no missing published studies omitted from the analysis. By using "Orwin's fail-safe N" with "random effects model" to assess whether publication bias affected the overall result. The analysis found that 20 additional studies with no effect of melatonin treatment will cause the p-value to be statistically non-significant (p> 0.05).

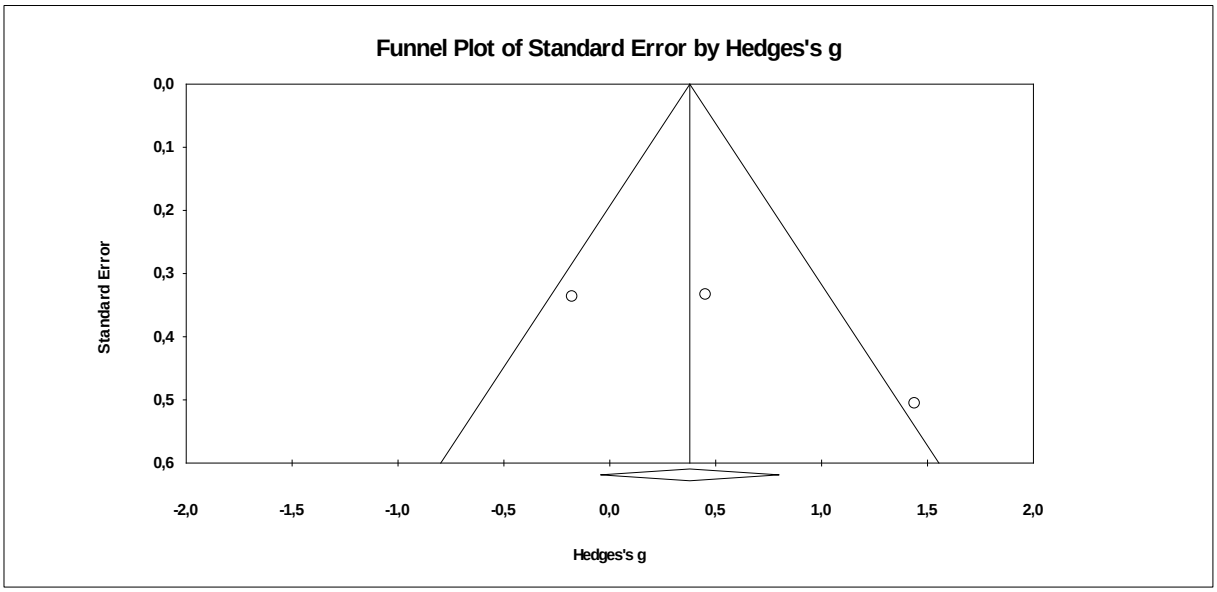

Figure 6. Funnel plot of sleep onset offset analysis

Analysis 5) Funnel plot of the analysis for total sleep time showed asymmetry, with some studies to the left, and several major studies around the average (Fig.7). Furthermore, by measuring how many studies are believed to exist, but not including, the "trim and fill", it was calculated that n = 0, indicating that there are no missing published studies omitted from the analysis. Use of "Orwin's fail-safe N" with "random effects model" to assess whether publication bias affected the overall result. This analysis could not be implemented.

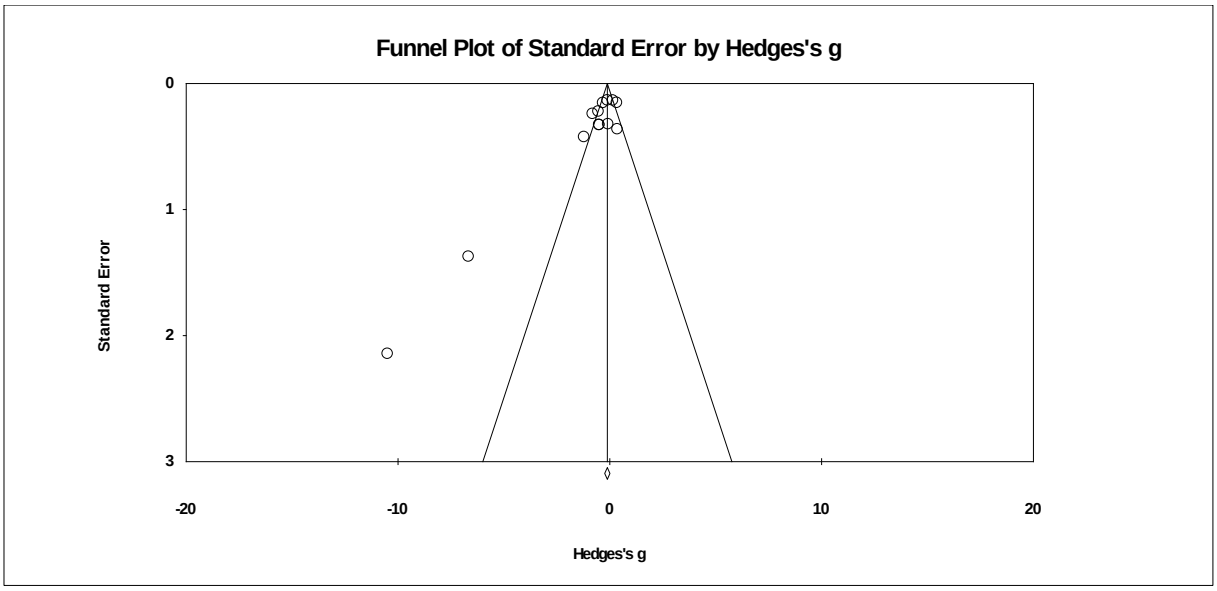

Figure 7. Funnel plot of total sleep time analysis

Discussion

Main findings

This meta-analysis evaluated the effectiveness of exogenous delivered melatonin in advancing the circadian sleep rhythm, or sleep timing in patients with DSPS. The weighted summarized effect size indicated that melatonin provides an advancement effect. Four of the five analyzed sleep parameters showed a significant effect in the correct direction. The present meta-analysis, however, contained a low number of studies which reduces the generalizability of the results, and making the effects more prone to change by inclusion of new studies compared to meta-analyzes containing a higher number of studies (Borenstein et al., 2009).

Changes in dim light melatonin (DLMO) following intervention found a large effect (0.77) compared with placebo treatment effect (-0.19). This strong effect has occurred as a result of the effectiveness of melatonin in patients diagnosed with DSPS. Only one of the studies included contained a low effect size and no significance (Smits et al., 2001), while the remaining studies contained strong effect sizes and high significance. However, 39 more studies of zero effect would be needed to produce non-significant results.

Measurement of sleep onset latency (SOL) in the intervention group showed a moderate effect (0.61) of melatonin treatment, compared with the placebo group in which the effect was non-significant (-0.08). Four studies (van der Heijden et al., 2005; van der Heijden et al., 2007; Rahman et a., 2009; Wasdell et al., 2007) included in the intervention group showed statistically significant improvement in SOL, which indicates that it took less time to fall asleep after participants went to bed, while two studies (Mundey et al., 2005; Rahman et al., 2010) barely showed improvement following melatonin treatment. 53 more studies of zero effect would be needed to produce non-significant results.

Changes in sleep onset time following intervention resulted in a significant and moderate effect (0.34), compared to the placebo group which found a slight negative and non-significant effect (-0.17). Taking melatonin was beneficial by advancing the sleep onset time, thus indicating that melatonin helps adjust the timing or sleep to become more in accordance with social rhythms (like job or education). Three of the included studies (van der Heijden et al., 2007; Oldani et al., 1994; Smits et al., 2001) reported moderate to strong results, whereas two studies (Oldani et al., 1994; van der Heijden et al., 2007) showed weaker effect. Six more studies of zero effect would be needed to produce non-significant results.

Sleep offset time measured in the intervention group resulted in a strong and significant effect (0.76), compared with placebo group who received a weak, negative and non-significant effect (-0.17). The intervention group included two studies (N= 15) whereas only one (Oldani et al., 1994) was significant, providing a moderate positive effect combined. The placebo group consisted of one study (Mundey et al., 2005), including three participants. Hence the small sample size in intervention and placebo group, the findings must be interpreted cautiously when it might be incorrect. Nevertheless, the findings suggest that sleep offset time is advanced as a result of melatonin treatment. Twenty more studies of zero effect would be needed to produce non-significant results.

The amount of total sleep time was however unaffected by the intervention. Although the placebo group showed a low negative, significant effect (-0.25), total sleep time was clearly less relevant as an indicator of the treatment effect. The between study variance was however extremely large for this parameter as one study (Rahman et al., 2010) showed a very strong and negative effect in both the intervention (-6.63) and placebo (-10.45), while another (Oldani et al., 1994) barely showed any effect at all (-0.04).

Heterogeneity in DLMO and sleep onset time was found to be weak but significant, indicating that the treatment effect varies between studies. By finding and examining

predictor variables it is possible to determine the cause of the changes, which would have been beneficial. However, there are few studies available in order to perform analyzes to elucidate the cause of the variation.

Variation between studies has probably not occurred by chance, but rather demonstrates that studies are different because they retrieved data from different populations, or a possible error variance within studies (study within error). In this case, the observed heterogeneity may seem to be influenced by both elements. No measurements can be assumed to be completely accurate and it is not possible to control for all conditions, thus the possibility of error variance is always present (Borenstein et al., 2009). Reviewing the characteristics of the included studies reveals that the studies come from different populations, e.g., adults and children, different doses of melatonin and administration time.

The overall purpose of the present meta-analysis was to statistically calculate whether there was any effect of exogenous melatonin treatment in patients with DSPS. Findings from the analysis proved that there was a statistically improved efficacy in several sleep parameters. Melatonin's effect on DLMO, SOL, sleep onset time and sleep offset time was significantly improved, compared with the placebo group which resulted in non-significant effects.

Total sleep time had no significant effect in the intervention group, whereas placebo group found a negative significant effect. This effect is supported by the meta-analysis of van Geijlswijk et al (2010), where their findings indicated a prolongation of the sleep length in children, but not in adults. In their analysis, there were twice as many children (N = 226) than adults (N = 91), which may have caused non-significant effect in adults.

Present findings is verified by another meta-analysis (van Geijlswijk et al., 2010), demonstrating melatonin to significant advance DLMO when comparing with baseline. They divided their analysis in children and adults, where both groups experienced significantly

advance in DLMO. Although melatonin has shown two advance DLMO, there are several aspects concerning DLMO to discuss. DLMO measurements are useful in diagnosing DSPS, since it occurs later in individuals with the disorder. A delayed DLMO does not necessarily develop as a result of the disorder, but may result from other conditions such as jet lag and shift work. In addition, melatonin onset and melatonin levels change with age (Littner, Hirshkowitz, Davila, Anderson, Kushida, Woodson, Johnson, & Wise, 2002).

The moderate and significant results found in the analysis of SOL are confirmed by another meta-analysis (Ferracioli-Oda, Qawasmi, & Bloch, 2013), which was demonstrated by comparison of intervention and placebo group, that melatonin has a significant benefit in reducing SOL. On the other hand, van Geilswijk et al. (2010) also found significant reduction of SOL in children, but not in adults. When children and adults were combined, results indicated an overall significant reduction in SOL, which confirms our results. In addition, Buscemi, Vandermeer, Hooton, Pandya, Tjosvold, Hartling, Baker, Klassen, and Vohra (2005) found both clinical and statistically significant enhanced effects in their measurements of melatonin intervention in SOL. Their analysis contained a lower number of subjects, less than 30 participants, which suggests that the comparison with their results should be done with caution.

van Geilswijk et al. (2010) found opposite of present study's results when analyzing sleep offset time. Their findings indicated no statistically significant effects in sleep offset time, either in children or adults. They concluded that melatonin does not affect sleep offset time. In their analysis, there were 99 participants included, whereas in present analysis only 15 participants were included. This low number of participants constructs weak and uncertain results, and conclusions must be drawn with a high degree of caution. Small numbers of participants increases the risk of type II statistical errors, involving an improper retain of the null hypothesis (Mittendorf, Arun, & Sapagay, 1995).

Differences in the analyzes of sleep onset time, sleep offset time and total sleep time between children and adults, can probably be attributed to parenting rules for bedtime. For example, van Geilswijk et al. (2010) conclude that melatonin treatment of total sleep time seem to work for children, but do not have the same effect on adults. This conclusion is not necessarily correct, because children usually have regular bedtimes set by the caregiver, while parents can decide for themselves. After reading the characteristics, some of the studies included in the present meta-analysis mentions declared bedtimes, while others do not. In addition, it can be large differences between weekends and weekdays, at what time children and adults go to bed, and how long they sleep. This may have influenced the analysis of sleep parameters, when this analysis has not analyzed children and adults separately.

The evidence found in advancing sleep-wake cycle are comparable with the study of van Geilswijk et al. (2010), but opposite from Buscemi et al. (2005), which could not demonstrate the effectiveness of melatonin in conjunction with DSPS. Present study included eleven studies with a total of 486 participants, while the meta-analysis of Buscemi et al. (2005) included nine studies and a total of 197 participants, and meta-analysis of van Geilswijk et al. (2010) included nine studies and a total of 317 participants. Number of studies and participants do not seem to account for the difference between the findings of all three meta-analysis.

Implications

Given our findings, it is necessary to reflect about the limitations and implications in this study. Because of the small number of included studies, generalizability based on the results are weak.

Differences between findings in the present meta-analysis and the meta-analysis of van Geilswijk et al. (2010) might be related to the time of administration. Their analysis focused specifically on the chronobiotic properties of melatonin, whereas the present analysis

measured the hypnotic properties of melatonin. Investigation of the chronobiotic properties involves administrating of melatonin few hours before endogenous melatonin onset. van Geilswijk et al. (2010) highlights that advancement of biological clock may be statistically and clinically insignificant, if the time interval between melatonin administration and the endogenous melatonin onset is short. Melatonin administered too late in relation to endogenous melatonin onset, may cause melatonin levels to persist until early morning (Brzezinski et el., 2005). In the present meta-analysis, however, the time of administration of melatonin is not been taken into account, which is considered as a weakness of the study.

The different melatonin doses given vary between studies, and are not taken into account in the present meta-analysis. The effect of different melatonin doses could have been examined through a meta-regression, to see if they would have resulted in different effects on the sleep-wake cycle. Exogenous melatonin administered at the right time and in the right dose could shift the circadian rhythm (Sack, Auckley, Auger, Carskadon, Wright, Vitiello, & Zhdanova, 2007). Ferracioli-Oda, Qawasmi, & Bloch (2013) performed meta-regressions to investigate the relationship between efficacy, dose and intervention length. Their findings demonstrated a strong and significant effect between high melatonin doses and longer intervention time, which resulted in greater effect sizes in both SOL and total sleep time. However, the optimal dose is not yet established, and the doses given in studies are ranged from very low to very high. Findings in the present meta-analysis might have been different if the doses had been measured separately. This is considered as a weakness in the study, and further research should consider the effect of different doses, as it might result in large differences in effect.

The treatment duration may be important when considering the effect of melatonin. It should be mentioned that most of the studies included in this meta-analysis has relatively short treatment duration, about four weeks. Therefore, the measured effect might be a short-

term effect, and not long lasting effect on sleep-wake cycle. Studies with longer duration of treatment are therefore preferable, to investigate the long term effects of melatonin intervention.

Conclusion

Our findings may help guiding clinicians with the use of exogenous melatonin in treatment of patients with DSPS. This meta-analysis demonstrated that exogenous melatonin administered to patients with DSPS improve sleep parameters. These findings are supported by previous meta-analyzes in the field, which found similar results demonstrating the beneficial effects of melatonin. Further research should consider the time of administration, dose and long term effects of melatonin.

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