A randomized controlled trial with bright light and melatonin for treatment of delayed sleep phase disorder. Effects on subjective and objective sleepiness and cognitive function.

Short running title:

RCT with bright light and melatonin for treatment of DSPD

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Abstract

Delayed sleep phase disorder (DSPD) is a circadian rhythm sleep disorder. Patients with DSPD have problems initiating sleep if they go to bed at a conventional time and they often have problems waking at desired times. If they rise early in the morning they usually experience severe sleepiness during morning hours. In the present study we investigated short- and long term effects on measures of subjective and objective sleepiness and cognitive function of bright light and melatonin treatment alongside gradually advanced rise times in adolescents and young adults. Four treatment conditions were used in the short-term intervention (two weeks); dim light (placebo) + placebo capsule, bright light + placebo capsule, dim light (placebo) + melatonin capsule and bright light + melatonin capsule. This was followed by a long-term intervention (three months) including two conditions; no treatment and combined bright light + melatonin treatment. Effects of treatment on sleepiness and fatigue were the primary outcome measures and effects on cognitive function were secondary outcome measures. On a gradual advancement of rise time schedule, all treatment conditions (bright light, melatonin, the combination and placebo) were almost equally effective in improving subjective daytime sleepiness, fatigue and cognitive function in the two-week study. The two-week intervention showed no effect on objective sleepiness. Long-term treatment increased some of the positive effects seen after two weeks. Combined bright light and melatonin treatment improved subjective daytime sleepiness, fatigue and cognitive function in the three-month study. The no-treatment group returned to baseline values on most variables. In conclusion, gradual advancement of rise times seems to produce positive effects on subjective sleepiness, fatigue and cognitive performance during short-term treatment of patients with DSPD. However, the benefits from gradually advanced rise times seem to wear off, suggesting that continuation of bright light and melatonin treatment is beneficial to maintain positive effects over time.

Key words: randomized controlled trial, circadian rhythms, delayed sleep phase disorder, bright light, melatonin, treatment, daytime function

Delayed sleep phase disorder (DSPD) is a circadian rhythm sleep disorder where the sleep period is delayed with respect to conventional norms (American Academy of Sleep Medicine 2005). Patients with DSPD have been described as unable to advance their sleep phase by behavioral means (American Academy of Sleep Medicine 2005), and the disorder is associated with impairments related to school or work functioning, alcohol and substance abuse and psychological and relational disturbances (American Academy of Sleep Medicine 2005; Dagan and Eisenstein 1999; Regestein and Monk 1995; Saxvig et al. 2012). Hence, DSPD is a disorder with several psychosocial challenges (Wilhelmsen-Langeland et al. 2012). The prevalence of DSPD is estimated to be 7-16% in adolescence (American Academy of Sleep Medicine 2005; Gradisar et al. 2011b).

DSPD does not involve a dysfunction of the sleep period itself, but simply a delay of the circadian rhythm (Thorpy et al. 1988; Weitzman et al. 1981). Thus, patients with DSPD have problems initiating sleep if they go to bed at a conventional time and they accordingly experience severe sleepiness during morning hours (American Academy of Sleep Medicine 2005; Thorpy et al. 1988; Weitzman et al. 1981). Our research group has previously shown that the sleep architecture itself is not different from healthy controls when patients with DSPD are allowed to sleep at self-chosen times (Saxvig et al. 2013b). Since the sleep period is delayed in patients with DSPD, they have more slow wave sleep between 6am and 8am than controls (Saxvig et al. 2013b). Sleep curtailment typically leads the patients to catch up on sleep when they can, i.e. by napping and by extending sleep on weekends and holidays, which only maintain and potentially increase the sleep phase delay the following nights (Crowley et al. 2007).

The effect of sleep deprivation is known to affect cognitive function negatively, but little is known about how these functions are influenced in patients with DSPD. Shekleton and colleagues (2010) have reviewed studies on neurobehavioral performance in patients with insomnia. The most consistent impairment was shown on tests measuring different aspects of attention and executive function, and their results called for the inclusion of standard psychometric tests in future studies of sleep disorders (Shekleton et al. 2010).

Successful advancement of the sleep period and circadian rhythm is expected to reduce or eliminate negative consequences such as daytime sleepiness in patients with DSPD (Gradisar et al. 2011a). Timed bright light exposure and melatonin administration seem to be the most widely used treatment options for DSPD in clinical practice (Bjorvatn and Pallesen 2009). The timing of light is crucial (Bjorvatn and Pallesen 2009) as light before core body temperature minimum (CTmin) delays the circadian rhythm, whereas light after CTmin advances the circadian rhythm (Khalsa et al. 2003). Bright light after awakening has proven to be effective in advancing the sleep phase in patients with DSPD (Lack et al. 2007; Rosenthal et al. 1990). Rosenthal and colleagues (1990) conducted the only study that we know of on patients with DSPD assessing the effects of bright light treatment on objective sleepiness (sleep propensity) by the multiple sleep latency test (MSLT) (Carskadon et al. 1986). Their bright light group (2500 lux) showed increased sleep latency at 9am and 11am (but not at other times during the day) compared to the dim light group (300 lux). Cole and colleagues (2002) found reduced subjective morning sleepiness in a bright light group (2700 lux masks) compared to a dim light group (<0.01 lux masks), but only in the most delayed subjects. Recently, cognitive behavioral therapy in combination with bright light therapy showed promising effects on advancement of the sleep period, subjective sleepiness and fatigue in adolescents with DSPD (Gradisar et al. 2011a).

Similar to the effects of light, the effects of exogenous melatonin administration also follow a phase-response curve (Lewy et al. 1998). Previous studies have shown that the sleep period may be advanced by use of melatonin in the evening, usually taken a few hours before expected sleep onset (Dahlitz et al. 1991; Kayumov et al. 2001; Mundey et al. 2005; Nagtegaal et al. 1998; Rahman et al. 2010). Only two of these studies included measures of subjective daytime sleepiness/alertness. Dahlitz and colleagues (1991) found no changes on self-reported alertness following melatonin treatment. Similarly, Kayumov and colleagues (2001) found no overall difference on measures of subjective sleepiness, fatigue and alertness between a melatonin and a placebo group. However, when adhering to an

imposed sleep schedule (midnight to 8am), subjects taking melatonin were less sleepy and fatigued than the placebo group.

There is currently not sufficient empirical evidence to recommend specific treatment guidelines for DSPD (Gradisar et al. 2011a) and more controlled studies are consequently warranted (Bjorvatn and Pallesen 2009; Gradisar et al. 2011a; Mundey et al. 2005). Despite the fact that DSPD is most common in adolescence and young adulthood, we only know of one treatment study on adolescents with DSPD (Gradisar et al. 2011a). In the present study we investigated short- and long-term effects on subjective and objective sleepiness and cognitive function of bright light and melatonin treatment alongside gradually advanced rise times in adolescents and young adults. The treatment protocol was designed based on knowledge of the advancing effects of melatonin and bright light on the circadian rhythm when timed correctly. The treatment protocol in the present study has been used for many years in clinical practice by some of the co-authors and is described in detail in a review (Bjorvatn and Pallesen 2009). The effects of four short-term treatment conditions were investigated; dim light (placebo)+ placebo capsule, bright light + placebo capsule, dim light (placebo)+ melatonin capsule and bright light + melatonin capsule. This was followed by a long-term intervention (approximately three months duration) including two conditions; no treatment and combined bright light + melatonin. In the present study we investigated the effect of treatment on subjective and objective daytime function (on a simulated real-life school/work-setting starting at 8am), with sleepiness and fatigue as primary outcomes and cognitive function as secondary outcome. Sleep data (sleep diary, actigraphy and DLMO) were also collected, but are described in another article (Saxvig et al., 2013a).

Methods

Participants

The participants were recruited to take part in a clinical trial (http://www.clinicaltrials.gov/: NCT00834886) through advertisements at high schools, a college and a university (i.e. e-mails, flyers, posters and stands) and in relevant media. A link to a study website was distributed, which contained information about the disorder, the study protocol and contact information.

Inclusion/exclusion criteria

Inclusion criteria were 1) living in Bergen, Norway, 2) age 16-25 years, 3) good general health as specified by the exclusion criteria (see below) and 4) fulfilling the diagnostic criteria for DSPD. The participants were diagnosed according to the criteria found in the International Classification of Sleep Disorders, 2nd version (ICSD-2) (American Academy of Sleep Medicine 2005), operationalized for this study as: 1) problems falling asleep in the evening, 2) falling asleep after 2 am at least 3 days a week, 3) ability to sleep until early afternoon, 4) problems waking up in time for school/work, 5) early wake-up times associated with extreme daytime sleepiness, 6) good subjective sleep quality and duration when given the opportunity to sleep at self-chosen times and 7) self-reporting verbally the aforementioned sleep problems as chronic (>6 months).The DSPD diagnosis was confirmed as required by the ICSD-2 criteria by sleep diary data covering a one week period showing a delayed sleep pattern.

Exclusion criteria were sleep disorders other than DSPD, moderate to severe psychopathology (see later for procedure), conditions assumed to affect sleep (i.e. migraine, B12 deficiency), all serious somatic disorders (i.e. rheumatoid arthritis, diabetes), medications or treatments assumed to affect sleep (i.e. sedative anti-histamines, antidepressants, hypnotics), substance abuse, night work, IQ < 70, breast feeding and pregnancy.

A total of 264 potential participants responded to the initial invitation. In total, 60 persons fulfilled the basic criteria for inclusion and were scheduled for a meeting. Of those, 10 withdrew prior to the scheduled meeting. The remaining 50 potential participants were screened with the Structured Clinical

Interview for DSM-IV (SCID-I) diagnoses (First et al. 1997), the IQ-test Raven`s Progressive Matrices (Raven 2000) and pregnancy test (only females) and further set up for a polysomnographic screening (PSG). A total of 40 participants (see Figure 1 for withdrawal/exclusion categories) were included and successively randomized for participation. Neither of the participants had ever before been diagnosed with DSPD nor had they previously received treatment for DSPD. Inclusion and data collection were performed from the fall of 2008 until early 2012. Figure 1 illustrates the participant flow throughout the study.

INSERT Figure 1

Ethics

Informed consent was obtained after a full explanation of the study protocol. For participants under 18 years of age, parents were required to sign the consent form before inclusion and to give verbal consent. All participants received a compensation fee (approximately 80$ USD) for their time invested in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway, the Norwegian Social Data Service and the Norwegian Medicines Agency.

Setting and facilities

All meetings with participants took place at the sleep laboratory at the Faculty of Psychology, University of Bergen. Inclusion meetings took place between 8am and 5pm, the polysomnography hook-up took place between 6pm and 1130pm. All daytime testing protocol meetings started 8-830am and ended about 2-3pm. Lighting conditions in the testing rooms were 200 lux. Light was set to 500 lux in the laboratory

where participants stayed during breaks. The laboratory had no windows. Hence, participants were not exposed to daylight while being tested. Although there are seasonal variations in daylight in Norway, these variations are likely to be spread across the sample and should consequently not influence the results. The first author (AWL) and co-author IWS administrated all tasks throughout the study (with help from a research assistant, co-author ØV).

Instruments

Demographic information

Data were collected regarding age, gender, self-reported average school grades, intelligence (Raven 2000), symptoms of anxiety and depression (Zigmond and Snaith 1983), school/employment status (high school or college/university students, employed or unemployed), living conditions (with or without their parents), bed time and rise time.

Subjective self-evaluations of sleepiness and fatigue

The Karolinska Sleepiness Scale (KSS) (Åkerstedt and Gillberg 1990) is a scale where subjects rate their concurrent sleepiness level. The scale is verbally anchored with steps ranging from 1 ("very alert") to 9 ("very sleepy, fighting sleep, effort to stay awake"). The Epworth Sleepiness Scale (ESS) (Johns 1991) is a questionnaire providing a trait measure of daytime sleepiness. The subject rates the probability of falling asleep/dozing off in eight different everyday situations on a scale ranging from 0 (no probability) to 3 (high probability). We used the validated Norwegian version of the ESS (Pallesen et al. 2007). For the Fatigue Questionnaire (FQ) (Chalder et al. 1993), we used a total fatigue score that was generated from 7 items related to physical fatigue and 4 items related to mental fatigue. We administered the validated Norwegian version of the FQ (Loge et al. 1998).

Objective sleepiness (arousal)

The Alpha Attenuation Test (AAT) is a quantitative method for assessing objective sleepiness. It is developed based on the fact that the EEG power spectrum in the alpha frequency band increases with eyes open and decreases with eyes closed as the participant becomes sleepier (Stampi 1995). The participants were instructed to sit comfortably in an office chair in a sound proof chamber, to relax but to remain awake and to look at a red "X" on the wall straight ahead of them. They were asked to close their eyes and to open their eyes consecutively at two-minute intervals, three times. Thus, the total duration of the AAT was 12 minutes. Electrodes were montaged according to the AASM Manual for the Scoring of Sleep and Associated Events (Iber et al. 2007). Data were collected online with ambulatory Embla Titanum recorders and the Somnologica software package (Embla Systems Inc., USA). A single EEG derivation was used for spectral analyses (O1). Power spectrum analysis criteria were set to: power-bands alpha = 8 - 11.99 Hz, 1 second epochs, 256 point fast Fourier transform (FFT) overlapped by 0%, where the FFT`s are averaged with the selected epoch duration. We divided the average spectral alpha power of eyes closed by the average spectral alpha power of eyes open, which gives a ratio of the "alpha attenuation coefficient" (AAC) (Stampi 1995). The higher the AAC is, the higher the alertness level is.

Cognitive function

The present study included a set of standardized psychometric tests to measure aspects of attention and executive function. The Conners` Continuous Performance Test (CPT-II) Version 5.1 for Windows® is a test of different aspects of attention (Conners and MHS Staff 2004). It lasts 14 minutes. The subject is instructed to press the space bar on the computer keyboard whenever a letter appears on the screen, except for the letter "X". The CPT-II is a test assessing the ability to maintain focused alertness over a relatively long period of time. In the present study we included an overall reaction time measure (RT for hits), two measures of accuracy (number of omission; responses that should have been given but were

not) and commissions (wrong responses given when there should be no response) and two measures of consistency (Hit RT standard error and Variability). Three subtests from Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler 1997); the Digit Symbol-, Letter-Number Sequencing- and the Symbol Search Test, were included as measures of working memory/processing speed. During the Digit Symbol Test, digits and symbols are presented as pairs and additional digits and symbols must be paired by the subject. Letter-Number Sequencing requires that the subject order numbers and letters that are presented in an unordered sequence. In the Symbol Search Test, the subject must match symbols that appear in different groups. Finally, three subtests from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al. 2001) were included as measures of executive function. From the Color Word Interference Test (CWIT) we included the third condition, where the subjects are presented color words printed in incongruently colored ink (CWIT-Inhibition), and the fourth condition, requiring the subject to switch between either naming the color of the incongruently colored color-words or reading the color names when presented with a brace (CWIT-Inhibition/Switching). From the Verbal Fluency Test (VFT), we included the condition where the subjects are asked to switch between reporting items from two different categories (VFT-Category Switching).

Compliance and side-effects

A form to be completed each day of the two-week treatment period was developed in order to measure compliance for timing/duration of light exposure and if capsule had been taken and at what time. Points were given for light exposure (one point), capsule taken (one point) and rise time (one point) at the prescribed time (+/- 1 hr). Full score on all measures was rated as 100% compliance. For the three-month follow-up, points were given for light exposure (yes=one point) and melatonin capsule taken (yes=one point). Full score was rated as 100% compliance. Side-effects during treatment were retrospectively recorded at the two-week assessment (participants noted any possible side-effects on a form developed for the study) and at three-month follow-up. In cases of adverse events, guidelines for Good Clinical Practice (GCP) were followed (Switula 2000).

Procedure/design

Participants underwent the same daytime testing protocol at three assessment points: before treatment (baseline assessment), after two-week treatment (two-week assessment) and after three months of treatment/no-treatment (three month assessment). Prior to baseline assessment, participants had been instructed to go to bed and rise at self-determined times for four consecutive days in order to avoid sleep deprivation. On the assessment days, the participants were instructed to rise at 7am and to meet at the sleep laboratory at 8am. Test sessions started about every hour from 9am to about 1pm with intermediate breaks, with the purpose of simulating a typical day at school or a day at work (between 8am and 9am the participants had breakfast and electrodes for the AAT were montaged). The AAT, KSS and CPT-II were all administered three times each assessment day, in the mentioned order, at approximately 9am, 11am and 1pm. All other tests were administered once. The protocol included measures of subjective sleepiness and fatigue (KSS, ESS and FQ), objective sleepiness/arousal (AAT) and performance on tests of cognitive function (CPT-II, WAIS-III subtests and D-KEFS subtests).

Participants were randomized into one of four treatment conditions lasting for two weeks in a double-blinded, placebo controlled design. The four treatment conditions were: dim light (placebo) and placebo capsules (placebo group), bright light and placebo capsules (bright light group), dim light (placebo) and melatonin capsules (melatonin group) and bright light and melatonin capsules (combination group). All groups were instructed to use dim/bright light and placebo/melatonin capsules on a gradual advancement schedule regarding rise times and treatment times. In a follow-up study, participants were re-randomized into two groups receiving either the treatment combination of bright light and melatonin alongside gradually advanced rise times (treatment group) or no treatment (no-treatment group) in an open label trial for approximately three months.

Treatment protocol

The treatment protocol was based on the approach described by Bjorvatn and Pallesen (2009). The participants were instructed to sleep until spontaneous awakening on the first day of treatment and then to expose themselves to the study light source for 30 to 45 minutes immediately after awakening, with eyes directed towards the lamp. Melatonin/placebo capsules were to be taken 12 hours after light treatment exposure was initiated. Because of the soporific effects of melatonin, capsules were not to be taken before 8pm in the evening. This instruction ensured that treatment was individualized according to how delayed each participant's circadian rhythm was. Rise time was advanced by one hour every day until the preferred rise time was reached (each participant chose their target rise time) and then maintained until the end of the two-week treatment period. If the participant overslept, the instructions were to be exposed to the study light lamp immediately upon awakening, to take a capsule 12 hours later and then advance by one hour every day until target rise time. No instructions were provided regarding bedtime. Alcohol usage was prohibited during the two-week treatment period; no instructions regarding alcohol use were given during the three-month follow-up study.

Bright white light and dim red light

Light lamps were ML-10 000 manufactured by Miljølys Inc., Norway. ML-10 000 is a light box (47 x 17.5 x 29 cm) containing three fluorescent bulbs (Philips, Ecotone, P1-L, RA-index=80, light temperature 4000 K). Lamplights were either bright white (approximately 10 000 lux at 50 cm distance) with a clear cover screen or dim (approximately 400 lux at 50 cm distance) with a red cover screen. Dim light lamps are traditionally assumed to have minimal effect on the endogenous circadian rhythm (Lewy et al. 1980) and dim light (300 lux) was used as the control condition in the study by Rosenthal and colleagues (1990), who found superior effects in their active condition (2500 lux).

Melatonin capsules and placebo capsules

Hard capsules were packed by Kragerø Tablettproduksjon Inc., Norway, for the two-week intervention, and contained either fast release melatonin (5-methoxy-N-acetyltryptamine) 3 mg or 3 mg of Maydis Amylum (maize starch). Melatonin was purchased from Nature's One, Asaman Inc., USA (www.asaman.com). We used the original capsules of 3 mg from Nature`s One for the three-month follow-up study.

Blinding

The two-week treatment study was double-blinded. Participants were informed that they would receive either red or white light, but not that the light intensity was different. Lamps were given to the participants packed in boxes concealing the color of the cover screen differentiated by a letter code (A and B) and the participants were instructed not to reveal the color to the study administrators at any time (blinding of light boxes was performed by two university employees not otherwise involved in the study). Participants were further informed that the capsules contained either melatonin or maize starch. The melatonin and placebo capsules were packed in identical containers differentiated by a number code (1 and 2). In case of adverse events, those who blinded the lamp boxes, kept the code for the capsules and the lamps throughout the data collection period. The three-month follow-up study was not blinded.

Randomization

The randomization lists were made (four groups for the two-week intervention, two groups for the three-month follow-up) using the Internet based program Research Randomizer (http://www.randomizer.org/form.htm). Participants were chronologically assigned to the respective groups on inclusion.

Statistical analyses

Data were analyzed using IBM SPSS Statistics version 19.0. In cases of withdrawal from the study or missing data, baseline values were carried forward in an intention to treat analysis to ensure that clinical effectiveness was not overestimated (Hollis and Campbell 1999).

Demographic variables were compared between groups using one-way ANOVA and *t*-tests for independent samples (age, self-reported school grades, intelligence, anxiety, depression, bed time and rise time) and Pearson chi square test (gender, high school/university or college, living situation) to investigate whether the groups differed on these parameters at baseline. One-way ANOVA was also performed on all outcome measures at baseline between the four two-week intervention groups and between the two three-month groups.

Effects of the two-week treatment period were compared between the four groups using two-way ANOVA (4 treatment groups x 2 assessment points) for repeated measures of KSS, AAT and CPT-II (values at all three sessions; 9am, 11am and 1pm). Only the mean values of the three sessions are presented in the tables, because no additional information was provided by analyzing each of them separately. Two-way ANOVA for repeated measures between baseline and two-week assessment was also performed for the WAIS-III subtests, the D-KEFS subtests and for the questionnaires (ESS and FQ). Raw scores (as opposed to scaled scores and t-scores relating to a normative average) were used for analysis of all cognitive performance tests (CPT-II, WAIS-III and D-KEFS). For compliance and measures of side-effects, one-way ANOVA (percentage of compliance) and chi square test (compliance ≥50% = yes/compliance <50% = no; side effect categories; and reported side effects = yes/did not report side effects = no) was performed to test for differences between the groups.

At three-month assessment the same variables were compared between the groups (no-treatment/treatment) with respect to both the baseline assessment and to the two-week assessment using

two-way ANOVA for repeated measures (2 treatment groups x 2 assessment points). Interaction effects were further assessed using *t*-tests for paired samples. Cohen`s d was calculated between baseline and the two-week assessment and between baseline and the three-month assessment using an online calculator (http://easycalculation.com/statistics/effect-size.php) with the formula: $d=M1-M2/(sqrt(SD_1^2+SD_2^2)/2)$.

Results

Baseline assessment

There were no differences in terms of demographic variables between the four groups in the two-week treatment study at baseline (Table 1). For the three-month follow-up, participants in the treatment group were somewhat older than the participants in the no-treatment group (p=.042) (Table 1). At baseline, there were no differences between the two-week groups or the three-month groups on any of the primary or secondary outcome measures.

INSERT TABLE 1

Two-week assessment

Subjective sleepiness and fatigue. At two-week assessment, all groups showed a reduction in subjective sleepiness measured with the KSS (p=<.0005). There were no interaction effect and hence no differential improvement on the KSS between the four groups (Table 2). Similarly, subjective sleepiness measured by the ESS showed effect of time (p=.028). All groups had improved subjective sleepiness measured by ESS at two-week assessment compared to baseline, but with no clear significant interaction. All four groups were less fatigued at two-week assessment with no interaction effect (Table 2).

Objective sleepiness/arousal. There were no differences between baseline and the two-week assessment on the AAC (Table 2).

INSERT TABLE 2

Cognitive performance. There was no effect of time or interaction on any of the CPT-II measures for reaction time or accuracy. There was an overall improvement over time on all working memory/processing speed variables (WAIS-III), but no interaction effect between the 4 groups was found (Table 3). There was no effect of time or interaction on CPT-II consistency measures. There was an overall improvement with time on all executive function measures (VFT-Category Switching, CWIT-Inhibition and CWIT Inhibition/switching) across all groups, with no interaction effect (Table 3).

INSERT TABLE 3

Dropouts, compliance and side-effects. Two participants withdrew from the two-week study (see Figure 1 for explanation). Compliance was 84.5% in the combination group, 77% in the melatonin group, 86.3% in the bright light group and 87.3% in the placebo group with no difference between the groups (p=.567). One participant in the combination group and two in the melatonin group were rated as non-compliant (<50%) (p=.306). Side-effects were reported by 15 participants. Of these 15, six were in the combination group, two in the melatonin group, four in the bright light group and three in the placebo group (p=.409).

Side-effects reported were headache (5), nausea (3), discomfort in eyes (5) and skin irritation (2). None of the side-effects were serious or long-lasting.

At two-week assessment there was advancement in rise time of almost two and a half hours and bedtime of about one hour across all groups, with no interaction effect (Saxvig et al 2013a).

Three-month assessment

Because there were no interactions differentiating the four treatment conditions at two-week treatment, the two-week data were therefore collapsed (two-week groups were combined) when they were used in the analysis for the three-month follow-up.

Subjective sleepiness and fatigue. At the three-month follow-up, there was an effect of time (p=<.0005) as well as an interaction effect (p=.022) on KSS in favor of the treatment group (Table 4). The treatment group reported reduced subjective sleepiness compared to baseline at all three time points (9am, p=.002; 11am, p=<.0005; and 1pm, p=.013). The no-treatment group did not score differently at three-month follow-up compared to baseline on any test session. Subjective sleepiness measured by the ESS showed a positive effect of time compared to baseline but no interaction. However, there was both an effect of time and an interaction effect when comparing the two-week- to the three-month assessment, revealing that the treatment group reduced their score over time (p=<.0005). The no-treatment group did not score differently on the ESS at three-month assessment compared to the two-week assessment (p=.180) (Table 4). There was an effect of time and an interaction effect on fatigue at three-month assessment compared to baseline. The treatment group was less fatigued (p=.004), while the no-treatment group scored no different from baseline on the fatigue scale (p=.894) (Table 4).

Objective sleepiness/arousal. There was no effect of time or interaction between the baseline and three-month assessment of the AAC (Table 4).

INSERT TABLE 4

Cognitive function. There was an interaction effect on the reaction time measure when comparing three-month follow-up to baseline (p=.010) and to two-week assessment (p=.011). The effect was due to slower RT for hits in the no-treatment group at three-month follow-up compared to baseline and to the two-week assessment, while the treatment group did not score differently than baseline at two-week or three-month assessment (Table 5). Three-month follow-up data showed that there was an improved effect of time from baseline on all working memory/processing speed variables. However, there was no interaction effect. There was also improvement over time at three-month follow-up compared to two-week assessment on the WAIS-III Digit Symbol Test, with no interaction effect (Table 5). There was an interaction effect on the CPT-II consistency measures Hit RT standard error and Variability (Table 5). The treatment group scored more consistent than the no-treatment group at three-month assessment compared to baseline. There was a positive effect of time on all executive function measures and an interaction effect on the VFT-Category Switching. Paired samples *t*-tests showed that the treatment group had improved their performance on VFT-Category Switching while the no-treatment group scored no different from baseline (Table 5).

INSERT TABLE 5

Dropouts, compliance and side-effects. Three participants withdrew from the three-month follow-up (see Figure 1 for explanation). Average compliance was 58% in the treatment group when including 19 participants (one missing value because compliance was not recorded by one participant). Thirteen participants (65%) were rated as compliant to treatment (≥50%) and seven (35%) as non-compliant (<50%). Side-effects were reported by three participants and regarded headache (1) and discomfort in eyes (2). Side-effects were not serious or long-lasting.

Three-month assessment showed an advancement in rise time of about two hours compared to baseline and bed-time of more than one hour in the treatment group, whereas the no-treatment group had returned to baseline timing of rise time and bedtime (Saxvig et al. 2013a).

Discussion

Effects of bright light and melatonin administered alongside gradual advancement of rise times were investigated using a randomized, double blind, placebo controlled design. After short-term treatment (two weeks), subjective sleepiness measured by the KSS was reduced across groups by more than one point with large effect sizes. However, there were no differences between the four treatment conditions. Two-week treatment also yielded reduction in subjective sleepiness in all groups assessed by the ESS, with a large effect size for the combination group only, and the treatment also resulted in a reduction on fatigue across the four groups. Participants in all four conditions improved their cognitive performance on tests of working memory/processing speed and executive function, but not on the reaction time, accuracy and consistency measures from the CPT-II. In sum, bright light, melatonin, the combination and placebo alongside a gradual advancement schedule were almost equally effective in improving subjective daytime sleepiness, fatigue and cognitive function in the two-week study. This contradicts the findings from previous studies, where subjective sleepiness, objective sleepiness, fatigue and alertness improved

significantly only after active treatment (Gradisar et al. 2011a; Kayumov et al. 2001; Rosenthal et al. 1990).

It has been assumed that patients with DSPD can not achieve advancement in sleep-phase (leading to reduction in daytime sleepiness) by behavioral means (American Academy of Sleep Medicine 2005). However, Sharkey and colleagues (2011) recently found that strict rise schedules could phase advance sleep in participants with delayed sleep phase. They did not assess sleepiness, but our findings suggest that also participants diagnosed with DSPD can achieve positive effects on subjective daytime sleepiness by gradual advanced rise times. Cole and colleagues (2002) did find a reduction in subjective morning sleepiness in the most delayed subjects, also in the dim light group, but the effect was larger after bright than dim light. Two-week treatment yielded no positive effects on objective sleepiness (AAT) in our study, in contrast to the findings by Rosenthal and colleagues (1990) of increased sleep latency on the MSLT during morning hours after bright light compared to dim light treatment. However, the AAT may be regarded mainly as a measure of arousal while the MSLT is a measure of sleep propensity; hence these two objective measures of physiological sleepiness may reflect different sleepiness modalities. In line with this, Alloway and colleagues (1997) found correlations between AAT and MSLT scores for a group of patients with narcolepsy but not for normal sleepers.

Long-term effects of bright light and melatonin were investigated using a randomized, controlled design for three months. The treatment group was less sleepy measured by the KSS compared to baseline and maintained the positive effect after short-term treatment at the three months follow-up. On the other hand, subjective sleepiness measures were no different from baseline measures in the no-treatment group; hence the positive effect of two-week treatment was eliminated when active treatment was terminated. Simultaneously, the treatment group had further reduced their subjective sleepiness measured by the ESS, from two-week- to the three-month assessment, and reported less fatigue after three-month treatment compared to baseline. These findings indicate that treatment of DSPD maintained longer than two weeks can lead to better effects on subjective sleepiness and fatigue. This is in line with suggestions by

Rosenthal and colleagues (1990) that maintained treatment is necessary, because otherwise the circadian rhythm tends to drift back to a delayed phase in patients with DSPD. Similar to the effects on subjective sleepiness, the treatment group had maintained advancement of rise time and bedtime after three-month treatment while the no-treatment group had drifted back to delayed rise- and bedtimes.

Strengths and limitations of the study

To our knowledge, this is the first study that systematically investigates the effect on daytime function of bright light and melatonin in the treatment of DSPD. Previous studies of effects of bright light have included behavioral instructions of advanced rise times, but no studies on the effect of melatonin have included a gradual advancement of rise times in their treatment protocol. This study is the first to assess both short- and long-term effects of treatment using a controlled design combining bright light, melatonin and gradual advanced rise time. It is also the first controlled study investigating the effect of bright light and melatonin on sleepiness and performance in adolescents and young adults diagnosed with DSPD. By holding the timing of the test sessions constant and in the morning, circadian confounding effects were reduced. Circadian variations in cognitive performance in relation to local and internal time have been shown for example in shift workers (Vetter et al. 2012).

The participants in the present study were thoroughly screened for other pathologies. Hence, anxiety, depression or attention disorders can thus be ruled out as probable confounders to our results. However, the results may, on the other hand, not be directly transferable to the large number of patients with DSPD who suffer from co-morbid disorders (Reid et al. 2012). Furthermore, our participants scored somewhat above average range on self-reported school grades and intelligence, which may represent a bias towards relatively well-functioning patients with DSPD compared to patients that we commonly meet in sleep clinics, e.g. those who have dropped out of school or who are unemployed because of their sleep disorder.

The conceptualization and operationalization of sleepiness are under constant debate in the research literature (Horne 2010). Because of this, we included a wide range of tests measuring different modalities of sleepiness and cognitive functions, believed to be transferable to performance during a day at school or a day at work. Although improvements seen across groups on tests of cognitive functions after two weeks are expected due to to a practice effect (Horne 2010; Van Dongen et al. 2003), it could not explain group differences. In addition, we cannot rule out that the improvements seen across the two-week groups were due to a placebo effect as all groups were active in following the instructions. Similarly, we cannot rule out that the differences seen across the groups in the three-month study were due to a placebo effect as only the treatment group received instructions and was an active group.

The sample size in the present study was quite large but the small group sizes in the four-armed two-week trial may still represent a limitation. There was a small age difference in the three-month follow-up groups, which possibly could account for some of the differences between the effects in the two groups. No other differences between background variables or baseline assessment were found; therefore it seems unlikely that the difference in age can explain the results.

As regards to the two-week treatment groups, the dim light lamps were used as placebo because they according to previous studies have no chronobiotic effect (Lewy et al. 1980; Rosenthal et al. 1990). However, more recent research has indicated that dim light at optimal times may have phase-setting effects (Duffy and Wright 2005). Light of 90-150 lux intensities has in recent studies been shown to have an effect on melatonin phase in healthy volunteers (Dijk et al. 2012), and it has been shown that long wavelength light has smaller effects on circadian phase than short-wavelength light (Wright et al. 2004). It is possible that the positive effects after the two-week assessment were due to the effect of light in all groups, and the behavioral instructions to gradually advance rise times in itself lead to earlier exposure to ambient light. Hence, what exactly is the reason why all groups improved on many variables after the two-week study is not clear. The fact that all groups in the two-week study (including the placebo-group) were active and given the same behavioral instructions, may differentiate them from pure wait-list

controls which has been used in other studies (Gradisar et al. 2011a). The no-treatment group in the three-month follow-up study had become familiar with the positive effects of a gradual advancement of rise times, but they were not encouraged or discouraged to continue this behavior. This fact, however, may differentiate them from a wait-list comparison group. We did not use statistical corrections for multiple comparisons in the analysis of cognitive function, but the conclusions in the present study are supported by the consistency of results within the different functional areas. Another limitation of the study was that we individualized target rise times in the treatment protocol, but did not record these, and can therefore not report how many participants reached and/or adhered to their target rise time.

In the two-week study, compliance was high across all groups and the lack of differentiating results between the active treatment groups and placebo cannot be attributed to differences in compliance. For the three-month treatment group, compliance was lower but still satisfactory from a clinical viewpoint. If compliance was higher and all participants in the three-month treatment group complied, the results might have been different. Our aim was to assess the effectiveness of a treatment modality that is readily available in for example a primary care setting with limited time per patient. Some patients (four of our participants were not compliant with instructions during the 3-month treatment) with DSPD will likely need closer follow-up in order to adhere to treatment.

Conclusion

Gradual advancement of rise times seemed to be effective in producing positive effects on subjective sleepiness, fatigue and cognitive performance in short-term treatment of DSPD. However, the benefits from gradually advancement of rise times seem to wear off, suggesting that continuation of bright light and melatonin treatment is beneficial to maintain positive effects over time.

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Figure legends:

Figure 1. Participation flow throughout the study.

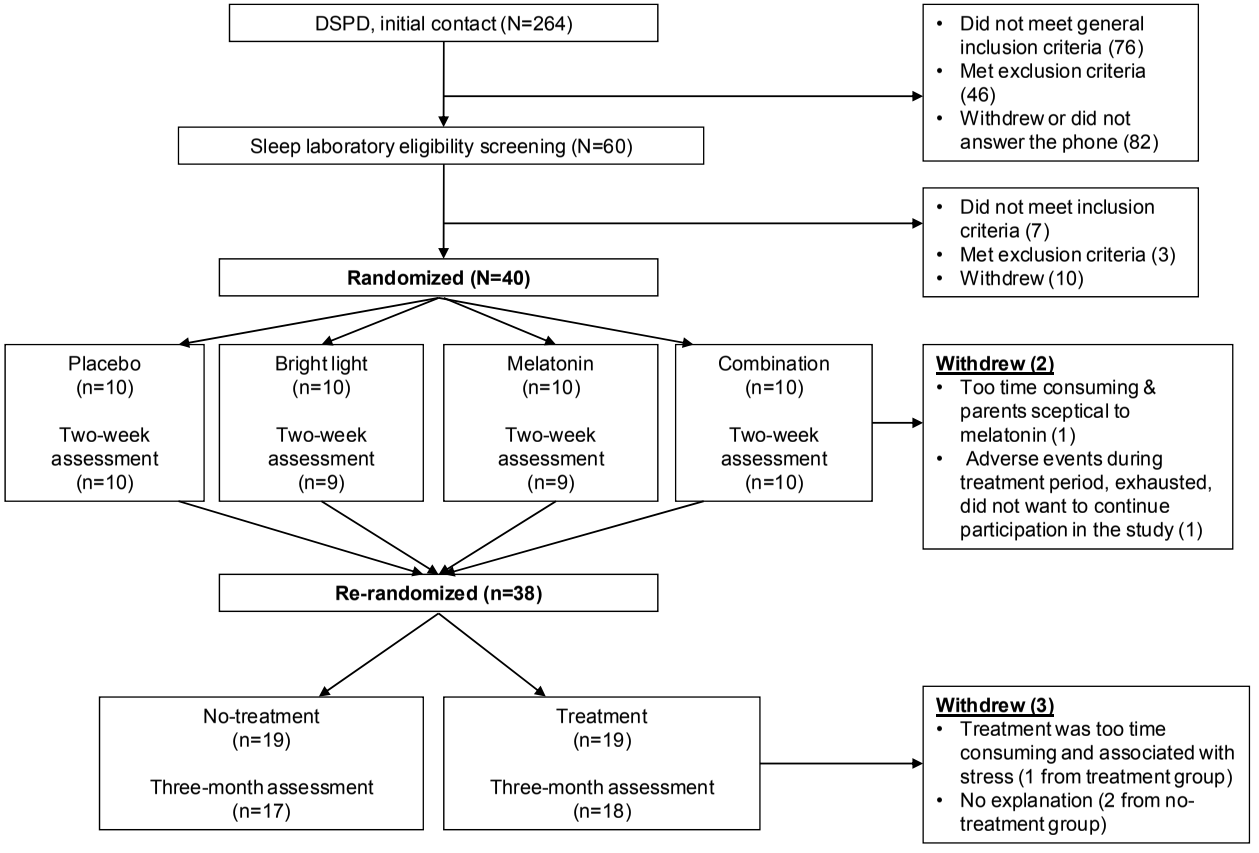

Figure 1. Participation flow throughout the study.

Table 1. Demographic information at baseline for the two-week intervention groups, the three-month follow-up groups and all participants (N = 40)

	Two-week intervention					Three-month follow-up			Total
	Placebo (n = 10)	**Bright light (n = 10)**	**Melatonin (n = 10)**	**Combination (n = 10)**	**P-value**	**No treatment (n = 20)**	**Treatment (n = 20)**	**P-value**	**All participants (N = 40)**
Age	20.8±3.4	20.7±3.4	21.2±2.7	20.3±3.3	p=.940	19.8±2.9	21.7±3.0	**p=.042**	20.7±3.1
Gender (male/female)	3/7	2/8	5/5	2/8	p=.414	5/15	7/13	p=.490	12/28
High school/ College/university	4/6	6/4	2/8	4/5×	p=.339	11/9	5/14×	p=.069	16/23
Live with/ without parents	4/6	3/7	2/8	3/7	p=.813	6/14	6/14	p=1.00	12/28
Grades#	4.3±0.5	4.5±0.6	4.5±0.4	4.0±0.9	p=.168	4.2±0.6	4.5±0.6	p=.228	4.3±0.6
Intelligence (IQ)	104.9±9.2	107.8±9.9	107.5±10.3	108.8±15.9	p=.894	107.8±12.1	106.7±10.7	p=.768	107.2±11.3
Depression†	4.0±2.5	2.1±1.0	2.5±2.6	2.9±2.6	p=.292	3.1±2.3	2.7±2.3	p=.637	2.9±2.3
Anxiety†	7.0±3.1	5.5±2.8	4.4±2.8	4.9±3.9	p=.306	5.4±3.7	5.5±2.7	p=.923	5.5±3.2
Bed time (hh:mm ± min)	02:24±129	02:40±130	02:10±58	02:04±118	p=.888	02:14±109	02:24±112	p=.779	02:19±109
Rise time (hh:mm ± min)	11:09±124	11:37±167	10:35±81	11:03±147	p=.779	10:55±137	11:16±126	p=.629	11:06±130

Two-week intervention: Placebo = dim light lamp and placebo capsules, Bright light = bright light lamp and placebo capsules, Melatonin = dim light lamp and melatonin capsules,
Combination = Bright light lamp and melatonin capsules
Three-month follow-up: No treatment = no instructions. Treatment = bright light lamp and melatonin capsules on a gradual advancement schedule
p-values from one-way ANOVA or Pearson chi-square test
× 1 participant in this group was employed
Self-reported average school grades were unavailable for three participants; one in the placebo group and two in the combination group; one in the no-treatment group and two in the treatment group (the scale ranges from 1-6, where 6 is the best possible grade)
† Measured by the Hospital Anxiety and Depression Scale (HADS)

Table 2. Subjective and objective sleepiness and fatigue in participants with DSPD before (baseline assessment) and after treatment (two-week assessment) with bright light and melatonin in a randomized, double blind, placebo-controlled design.

	Placebo (n = 10)		**Bright light (n = 10)**		**Melatonin (n = 10)**		**Combination (n = 10)**		**P-values**	
	Mean ± SD	d	Mean ± SD	d	Mean ± SD	d	Mean ± SD	d	Time	Group x time
Subjective sleepiness and fatigue										
Karolinska Sleepiness Scale										
Baseline assessment	7.5 ± 0.6		7.2 ± 1.1		7.2 ± 1.1		7.3 ± 0.7			
Two week assessment	6.5 ± 1.5	0.87	6.3 ± 1.8	0.60	5.9 ± 1.3	1.07	6.0 ± 1.6	1.05	**<.0005**	.887
Epworth Sleepiness Scale										
Baseline assessment	9.3 ± 4.9		9.4 ± 2.9		9.6 ± 4.6		13.2 ± 2.8			
Two week assessment	9.1 ± 4.0	0.04	8.9 ± 3.6	0.15	9.4 ± 4.7	0.04	10.1 ± 4.0	0.90	**.028**	.062
Fatigue Questionnaire										
Baseline assessment	14.8 ± 3.3		13.8 ± 3.0		14.6 ± 3.3		14.1 ± 2.8			
Two week assessment	14.8 ± 4.2	0.00	11.5 ± 3.8	0.66	14.1 ± 4.5	0.12	11.9 ± 3.0	0.74	**.036**	.384
Objective sleepiness										
Alpha Attenuation Coefficient×										
Baseline assessment	5.8 ± 5.2		6.0 ± 5.2		3.5 ± 2.8		3.4 ± 2.6			
Two week assessment	5.6 ± 4.9	-0.03	6.3 ± 5.1	0.05	4.7 ± 4.1	0.34	3.3 ± 2.6	-0.03	.470	.643

Placebo = dim light lamp and placebo capsules, Bright light = bright light lamp and placebo capsules, Melatonin = dim red light and melatonin capsules, Combination = bright light lamp and melatonin capsules

p-values: Overall 4x2 ANOVA, main effects of time (time) and interaction effects (group x time)

Time: Overall mixed between-within subjects 4x2 ANOVA (4 treatment groups x 2 time points); main effect of time

Group x time: Overall mixed between-within subjects 4x2 ANOVA (4 treatment groups x 2 time points); interaction effect

d: Cohen`s d for paired samples (a negative Cohen`s d indicates a worsened score compared to baseline)

× One missing at baseline assessment in the melatonin group due to technical failure, alpha attenuation coefficient could not be calculated because of too much artefacts

Table 3. Cognitive performance measures in participants with DSPD before (baseline assessment) and after treatment (two-week assessment) with bright light and melatonin in a randomized, double blind, placebo-controlled design.

	Placebo (n = 10)		**Bright light (n = 10)**		**Melatonin (n = 10)**		**Combination (n = 10)**		**P-values**	
	Mean ± SD	d	Mean ± SD	d	Mean ± SD	d	Mean ± SD	d	Time	Group x time
Cognitive function										
Reaction time										
CPT-II RT for hits										
Baseline assessment	313.1 ± 37.1		331.5 ± 42.5		303.2 ± 29.4		317.5 ± 38.2			
Two week assessment	321.1 ± 72.0	-0.13	324.7 ± 50.6	0.14	302.2 ± 49.7	0.02	321.6 ± 62.0	-0.07	.883	.897
Accuracy										
CPT-II Omissions										
Baseline assessment	9.2 ± 13.0		3.0 ± 3.1		6.6 ± 6.6		5.5 ± 7.7			
Two week assessment	20.0 ± 44.3	-0.33	4.9 ± 2.9	-0.63	5.3 ± 5.0	0.22	4.2 ± 4.0	0.21	.377	.375
CPT-II Comissions										
Baseline assessment	22.3 ± 6.5		17.1 ± 8.0		20.5 ± 6.9		18.7 ± 7.4			
Two week assessment	23.2 ± 8.1	-0.12	17.8 ± 8.6	-0.08	20.3 ± 5.8	0.03	19.6 ± 9.8	-0.10	.421	.939
Working memory/ Processing speed										
WAIS-III Digit Symbol Test										
Baseline assessment	78.5 ± 14.1		79.2 ± 10.0		85.1 ± 9.7		72.5 ± 14.2			
Two week assessment	87.1 ± 16.3	0.56	87.9 ± 12.0	0.78	95.9 ± 15.3	0.84	83.8 ± 17.3	0.71	**<.0005**	.825
WAIS-III Symbol Search										
Baseline assessment	36.4 ± 5.3		38.1 ± 5.9		39.4 ± 6.0		38.3 ± 7.8			
Two week assessment	43.4 ± 4.8	1.38	44.3 ± 7.6	0.91	45.9 ± 5.9	1.09	43.2 ± 8.1	0.61	**<.0005**	.843
WAIS-III Letter-Number Sequencing										
Baseline assessment	11.2 ± 2.3		10.8 ± 3.3		13.5 ± 2.6		11.4 ± 3.5			
Two week assessment	12.8 ± 3.4	0.55	11.8 ± 3.4	0.29	15.4 ± 2.6	0.73	13.3 ± 3.5	0.54	**<.0005**	.788
Consistency										
CPT-II Hit RT standard error										
Baseline assessment	7.0 ± 4.4		5.4 ± 2.8		5.8 ± 3.4		6.1 ± 3.5			
Two week assessment	9.7 ± 12.7	-0.28	5.6 ± 3.6	-0.06	5.6 ± 2.2	0.06	5.6 ± 1.4	0.18	.500	.455

CPT-II Variability											
Baseline assessment	13.9 ± 13.4		8.9 ± 8.2		12.7 ± 12.1		12.8 ± 14.2				
Two week assessment	21.3 ± 32.2	-0.30	9.9 ± 10.5	-0.10	10.3 ± 5.4	0.25	9.8 ± 5.2	0.28	.735	.260	
Executive function											
VFT-Category Switching											
Baseline assessment	14.9 ± 3.3		12.6 ± 1.4		13.5 ± 2.6		13.1 ± 2.2				
Two week assessment	15.5 ± 4.2	0.15	12.9 ± 1.4	0.21	15.2 ± 2.7	0.64	14.5 ± 2.6	0.58	**.016**	.566	
CWIT-Inhibition†											
Baseline assessment	52.6 ± 22.4		43.4 ± 8.2		43.5 ± 5.4		48.0 ± 10.0				
Two week assessment	42.0 ± 6.4	0.64	41.8 ± 8.1	0.19	39.2 ± 3.2	0.96	42.6 ± 11.2	0.48	**.002**	.304	
CWIT-Inhibition/Switching†											
Baseline assessment	54.6 ± 9.6		54.4 ± 8.6		52.0 ± 6.5		58.0 ± 11.3				
Two week assessment	47.9 ± 8.0	0.75	47.9 ± 9.8	0.70	45.1 ± 8.0	0.94	50.6 ± 10.3	0.68	**<.0005**	.981	

Placebo = dim light lamp and placebo capsules, Bright light = bright light lamp and placebo capsules, Melatonin = dim red light and melatonin capsules, Combination = bright light lamp and melatonin capsules

CPT-II = Conners` Continuous Performance Test, RT = reaction time, WAIS-III = Wechsler Adult Intelligence Scale-III, D-KEFS = Delis-Kaplan Executive Function System, CWIT = Color Word Interference Test, VFT = Verbal Fluency Test

p-values: Overall 4x2 ANOVA, main effects of time (time) and interaction effects (group x time)

Time: Overall mixed between-within subjects 4x2 ANOVA (4 treatment groups x 2 time points); main effect of time

Group x time: Overall mixed between-within subjects 4x2 ANOVA (4 treatment groups x 2 time points); interaction effect

d: Cohen`s d for paired samples (a negative Cohen`s d indicates a worsened score compared to baseline)

† One participant in the placebo group and one in the bright light group were colorblind and did not complete the test

Table 4. Measures of subjective and objective sleepiness and fatigue in participants with DSPD (delayed sleep phase disorder) at three-month follow-up compared to baseline assessment (Baseline – three-months) and to two-week assessment (Two-weeks† – three-months). During three-month follow-up, participants received either no treatment (no-treatment group) or treatment with bright light and melatonin on a gradual advancement schedule (treatment group).

	No treatment (n = 20)		**Treatment (n = 20)**		**P-values Baseline - three-months**		**P-values Two-weeks^ - three-months**	
	Mean ± SD	d	Mean ± SD	d	Time	Group x time	Time	Group x time
Subjective sleepiness and fatigue								
Karolinska Sleepiness Scale								
Baseline assessment	7.5 ± 0.8		7.2 ± 1.0					
Two-week assessment	6.5 ± 1.7		5.9 ± 1.3					
Three-month assessment	7.0 ± 1.5	0.41	5.6 ± 1.7*	1.14	**<.0005**	**.022**	.782	.067
Epworth Sleepiness Scale								
Baseline assessment	11.5 ± 3.7		9.3 ± 4.3					
Two-week assessment	10.1 ± 3.5		8.7 ± 4.3					
Three-month assessment	9.2 ± 4.3	0.57	5.4 ± 3.3#	1.02	**<.0005**	.165	**<.0005**	**.026**
Fatigue Questionnaire								
Baseline assessment	15.0 ± 3.2		13.7 ± 2.9					
Two-week assessment	14.1 ± 4.6		12.1 ± 3.3					
Three-month assessment	14.8 ± 5.8	0.03	10.0 ± 3.7*	1.12	**.019**	**.029**	.386	.077
Objective sleepiness								
Alpha Attenuation Coefficient×								
Baseline assessment	4.5 ± 4.1		4.9 ± 4.3					
Two-week assessment	4.6 ± 4.2		5.3 ± 4.5					
Three-month assessment	3.9 ± 3.5	-0.15	5.6 ± 4.5	0.15	.992	.238	.292	.073

p-values: Main effects of time (Time) and interaction effects (Group x time) by overall 2x2 ANOVA between 2 assessment points

d: Cohen`s d for paired samples between baseline assessment and three-month assessment (a negative Cohen`s d indicates a worsened score compared to baseline)

*p<.05 based on paired samples t-tests within each group compared to baseline assessment

# p<.05 based on paired samples t-tests within each group compared to two-week assessment

^Data from the four two-week treatment groups were collapsed in the analysis

× One missing at baseline assessment in the treatment group due to technical failure, alpha attenuation coefficient could not be calculated because of too much artefacts

Table 5. Measures of cognitive performance in participants with DSPD (delayed sleep phase disorder) at three-month follow-up compared to baseline assessment (Baseline – three-months) and to two-week assessment (Two-weeks† – three-months). During three-month follow-up, participants received either no treatment (no-treatment group) or treatment with bright light and melatonin on a gradual advancement schedule (treatment group).

	No treatment (n = 20)		**Treatment (n = 20)**		**P-values Baseline-three-months**		**P-values Two-weeks^-three-months**	
	Mean ± SD	d	Mean ± SD	d	Time	Group x time	Time	Group x time
Cognitive function								
Reaction time								
CPT-II RT for hits								
Baseline assessment	317.5 ± 37.7		315.1 ± 37.4					
Two-week assessment	319.5 ± 56.9		315.3 ± 59.9					
Three-month assessment	341.3 ± 68.8*#	-0.42	306.4 ± 38.9	0.22	.218	**.010**	.271	**.011**
Accuracy								
CPT-II Omissions								
Baseline assessment	4.9 ± 5.9		7.3 ± 10.2					
Two-week assessment	5.3 ± 4.7		11.8 ± 31.6					
Three-month assessment	10.6 ± 20.1	-0.38	6.0 ± 9.4	0.13	.263	.077	.929	.105
CPT-II Comissions								
Baseline assessment	18.6 ± 7.4		20.6 ± 7.1					
Two-week assessment	19.5 ± 8.7		20.9 ± 7.7					
Three-month assessment	18.0 ± 8.9	0.04	20.6 ± 8.6	0.00	.668	.744	.215	.459
Working memory/ Processing speed								
WAIS-III Digit Symbol Test								
Baseline assessment	78.2 ± 14.9		79.5 ± 10.2					
Two-week assessment	87.2 ± 15.9		90.2 ± 15.2					
Three-month assessment	89.2 ± 16.1	0.70	95.0 ± 16.4	1.13	**<.0005**	.155	**.023**	.346
WAIS-III Symbol Search								
Baseline assessment	37.9 ± 6.7		38.2 ± 5.4					
Two-week assessment	43.1 ± 7.2		45.3 ± 5.9					
Three-month assessment	43.9 ± 7.4	0.85	46.9 ± 6.8	1.41	**<.0005**	.377	.435	.931
WAIS-III Letter-Number Sequencing								

Baseline assessment	11.5 ± 3.4		12.0 ± 2.8					
Two-week assessment	13.3 ± 3.4		13.4 ± 3.4					
Three-month assessment	13.4 ± 3.1	0.58	14.5 ± 3.2	0.83	**<.0005**	.514	.105	.179
Consistency								
CPT-II Hit RT standard error								
Baseline assessment	5.6 ± 3.2		6.6 ± 3.8					
Two week assessment	5.8 ± 2.9		7.5 ± 9.1					
Three month assessment	7.0 ± 4.1*	-0.38	6.2 ± 4.1	0.10	.175	**.024**	.964	.133
CPT-II Variability								
Baseline assessment	11.2 ± 11.5		13.1 ± 12.4					
Two-week assessment	11.0 ± 8.8		14.7 ± 23.2					
Three-month assessment	15.6 ± 15.9*	-0.31	12.2 ± 13.1	0.07	.160	**.039**	.643	.136
Executive function								
VFT-Category Switching								
Baseline assessment	13.1 ± 2.3		14.0 ± 2.7					
Two-week assessment	13.5 ± 2.3		15.6 ± 3.3					
Three-month assessment	13.4 ± 2.6	0.12	15.7 ± 2.2*	0.69	**.003**	**.043**	1.0	.793
CWIT-Inhibition†								
Baseline assessment	48.1 ± 17.5		45.5 ± 6.7					
Two-week assessment	43.8 ± 8.7		39.0 ± 5.5					
Three-month assessment	44.3 ± 9.6	0.26	40.5 ± 5.5	0.81	**.005**	.695	.229	.534
CWIT-Inhibition/Switching†								
Baseline assessment	56.0 ± 8.9		53.4 ± 9.3					
Two-week assessment	49.4 ± 8.5		46.4 ± 9.4					
Three-month assessment	50.7 ± 9.0	0.59	44.7 ± 7.3	1.04	**<.0005**	.140	.895	.137

CPT-II = Conners` Continuous Performance Test, RT = reaction time, WAIS-III = Wechsler Adult Intelligence Scale-III, D-KEFS = Delis-Kaplan Executive Function System, CWIT = Color Word Interference Test, VFT = Verbal Fluency Test

p-values: Main effects of time (Time) and interaction effects (Group x time) by overall 2x2 ANOVA between 2 assessment points

d: Cohen`s d for paired samples between baseline assessment and three-month assessment (a negative Cohen`s d indicates a worsened score compared to baseline)

*p<.05 based on paired samples t-tests within each group compared to baseline assessment

# p<.05 based on paired samples t-tests within each group compared to two-week assessment

^Data from the four two-week treatment groups were collapsed in the analysis

† One participant in the no-treatment group and one in the treatment group was colorblind and did not complete the test