Delayed Sleep Phase Disorder

Prevalence, Diagnostic aspects, Associated factors and Treatment concepts

KATARINA DANIELSSON
Abstract

Delayed sleep phase disorder (DSPD) is the most common circadian rhythm sleep disorder. Persons with DSPD have great difficulties falling asleep and waking up at conventional times. To diagnose DSPD this delayed sleep-wake rhythm should cause social impairment and distress for the individual. Evening melatonin and morning bright light are the recommended treatments. The overall aim of this thesis was to evaluate at-home treatment with Light therapy (LT) and the feasibility of adding cognitive behavior therapy (CBT) to LT in DSPD, furthermore prevalence, diagnostic aspects and associated factors were investigated.

Study I included 673 randomly selected individuals aged 16–26 years. The prevalence of DSPD was 4.0%. Unemployment (defined as an absence of educational or work activities) and an elevated level of anxiety were associated with DSPD.

In study II, dim light melatonin onset (DLMO) was measured in healthy adults. Time for DLMO DLMO (Mean±SD) was 20:58±55 minutes.

Studies III, IV, and V present results from a randomized controlled trial examining the feasibility of CBT as an additive treatment to LT with scheduled rise times, in persons with DSPD. Sleep onset and sleep offset was significantly advanced from baseline (03:00±1:20; 10:22±2:02 respectively) to the end of LT (01:27±1:41; 08:05±1:29, p<0.001 respectively). This advancement was predicted by consistent daily usage of the LT-lamp. At the follow-ups after LT and CBT or LT alone, sleep onset remained stable, sleep offset was delayed, and sleep difficulties were further improved, but there was no significant group interaction over time. There was a significant group interaction over time in the severity of anxiety and depressive symptoms, both in favor of the LT+CBT group.

Conclusively, DSPD was common among adolescents and young adults and it was associated with unemployment and elevated levels of anxiety. DLMO appeared in the expected time range in healthy working adults. At-home treatment with LT with scheduled rise times advanced sleep-wake rhythm and improved sleep difficulties in DSPD. Even though sleep-wake rhythm was not further advanced or better preserved in the participants that received LT+CBT compared to LT alone, the addition of CBT to the treatment regimen was feasible and well accepted.

Keywords: delayed sleep phase disorder, prevalence, diagnostic aspects, associated factors, light therapy and cognitive behavior therapy

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This Thesis is dedicated to my Grandmother and Grandfather
Greta and Viking Eklund
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Contents

Introduction ................................................................................................... 11

Background ................................................................................................... 12
  Sleep regulation ........................................................................................ 12
  Melatonin “the hormone of darkness” ..................................................... 12
  Sleep during puberty ............................................................................. 14

DSPD ........................................................................................................ 14
  Diagnosing DSPD ............................................................................. 15
  Assessing circadian phase in DSPD .................................................... 16
  Prevalence of DSPD ......................................................................... 18
  Social impairment and psychiatric comorbidities observed in DSPD. 18
  Pathogenesis of DSPD ................................................................... 19
  Personality profile and psychological aspects of DSPD ..................... 20
  Treatment of DSPD ........................................................................ 20

Aims and scope ............................................................................................. 24

Method .......................................................................................................... 25
  Study design ..................................................................................... 25
  Participants ....................................................................................... 25
    Protocol failures in study III, IV and V ........................................... 27
  DSP and DSPD criteria in study I ....................................................... 29
  Ethics .................................................................................................... 29
  Measures ............................................................................................. 29
    Dim Light Melatonin Onset (DLMO) .............................................. 29
    Questionnaires ............................................................................... 30
  Interventions ..................................................................................... 32
    Light therapy (LT) .......................................................................... 32
    Scheduled rise times ..................................................................... 33
    Cognitive Behavior Therapy (CBT) ................................................ 33
  Statistics ............................................................................................. 35

Results ........................................................................................................... 37
  Prevalence of DSPD and correlations with sleep related questions...... 37
  Factors associated with DSP versus no delayed sleep phase .......... 40
  Factors associated with DSPD versus no delayed sleep phase ....... 41
  Factors associated with DSP versus DSPD ........................................ 41
Abbreviations

CBT  Cognitive behavioral therapy
CI   Confidence interval
CRSD Circadian rhythm sleep disorder
DLMO Dim light melatonin onset
DSM-5 Diagnostic and statistical manual of mental disorder, 5th Ed
DSP  Delayed sleep phase
DSPD Delayed sleep phase disorder
ESS  Epworth Sleepiness Scale
ICSD International Classification of Sleep Disorders
ISI  Insomnia Severity Index
HADS-A Hospital Anxiety and Depression Scale (anxiety subscale)
HADS-D Hospital Anxiety and Depression Scale (depression subscale)
LT   Light therapy
M    Mean
MEQ  Morningness-Eveningness Questionnaire
NT   No Treatment
OR   Odds ratio
PSWQ Penn State Worry Questionnaire
SCN  Suprachiasmatic nuclei
SD   Standard deviation
SRS  Symptom-Focused Rumination Scale
Sleep is an important part of our lives, and sleep difficulties are associated with both physical and mental illness. There are a variety of reasons for sleep difficulties, including other conditions (e.g., chronic pain, anxiety, depression), stress in our social environment, and sleep disorders, or a combination of all three. Diurnal rhythms exhibit a delay during puberty in humans. If this delayed sleep-wake rhythm is persistent and causes insomnia symptoms or excessive daytime sleepiness and distress or impairment for the affected individual, it is regarded as delayed sleep phase disorder (DSPD).

Persons with DSPD are often misdiagnosed, and it can be difficult to separate a DSPD from insomnia, normal sleep during puberty, and hypersomnia. It is important to use a sleep diary including workdays and days off when diagnosing DSPD. A person with DSPD has great difficulties falling asleep at conventional bed times which in some cases can cause a conditioned insomnia. However if the DSPD person are able to choose their own sleep-wake rhythm their sleep will be of normal duration and quality, which differs them from the person with insomnia. This differentiation is important since there are different treatments recommendations for Insomnia compared to DSPD. In insomnia CBT and sometimes hypnotic drugs are the recommended treatments whereas for DSPD morning bright light and evening melatonin are the most recommended treatments.

Clinical trials are sparse in DSPD and DSPD management is often complicated by a high frequency of relapses, poor compliance, and accompanying insomnia, anxiety, and depressive symptoms. Therefore the overall aim of this thesis was to evaluate at-home treatment with Light therapy (LT) and the feasibility of adding cognitive behavior therapy (CBT) to LT in DSPD, furthermore prevalence, diagnostic aspects and associated factors were investigated.
Background

Sleep regulation

Sleep is regulated by endogenous factors, which primarily influence sleep quantity, and homeostatic factors, which primarily influence sleep quality (Dijk et al., 1990). Diurnal rhythm is controlled by the circadian clock, which consists of two nuclei in the brain called the suprachiasmatic nuclei (SCN) (Moore, 1997). The SCN are located in the middle of the brain, in the anterior part of the hypothalamus, just above the chiasma. They receive signals about light and darkness primarily from intrinsically photosensitive retinal ganglion cells, through the light-sensitive pigment melanopsin, (Brainard et al., 2001). Information about time of the day is forwarded to the rest of the body from the biological clock through secretion of melatonin from the pineal gland. Most individuals have a well-installed biological clock with an intrinsic period of 24h and 11 minutes, when there are no influences of time cues (Czeisler et al., 1999). The secretion of melatonin starts in the evening, reaches its peak around 3 o’clock at night, and decreases until the morning (Lynch et al., 1975).

Melatonin “the hormone of darkness”

Melatonin was first characterized in 1958 (Lerner & Lerner, 1958), while looking for the most skin-lightening factor known to be present in the pineal gland. In 1978, the sleep-inducing effect of melatonin was discovered (Lerner & Nordlund, 1978). Melatonin can be seen as a circadian coupling agent, desynchronizing central and peripheral clocks and optimizing phase with respect to external time cues, optimizing cellular and system processes, and augmenting defense systems (Arendt, 2005).

L-tryptophan is the precursor of serotonin which in turn can convert into melatonin see Figure 1. The rate-limiting enzyme aralkylamine N acetyltransferase is important in the synthesis of melatonin. This enzyme has a much stronger activity and exhibition in humans during the night and it is inhibited by light (Coon et al., 2002; Klein et al., 1997). The most important external factor that can change melatonin secretion is light/darkness. This is the reason why melatonin is known as “the hormone of darkness”.
The onset of melatonin secretion at dusk promotes activity in nocturnal (night active) animals and sleep in diurnal animals, including humans.

Even though the melatonin profile (timing and amplitude) is highly reproducible from day to day and week to week, rather like a hormonal fingerprint (Arendt, 1988, Klerman et al., 2002,) there are seasonal variations in the human melatonin profile, with an earlier phase in summer (Bojkowski and Arendt, 1988; Broadway et al, 1987), higher amplitude during winter (Morera & Abreu, 2006) and, according to a report (Kauppila et al, 1987), increased concentration and duration of secretion in winter in high latitudes. Evidence also indicates that the amplitude of melatonin is blunted during the luteal phase of the menstrual cycle (Baker & Driver, 2007; Wetterberg et al, 1999).

The plasma melatonin amplitude has its peak during puberty and after that the excretion declines in adults with age, as does the amplitude of the plasma melatonin (Iguichi et al, 1982; Zhao et al, 2002; Zhou et al, 2003). Furthermore there are various substances and pathological conditions that can influence melatonin (Claustrat et al, 2005; Zeitzer et al., 1999).
Sleep during puberty

During puberty, delays in sleep-wake rhythm and circadian rhythm have been observed in both humans and other mammals (Carskadon et al, 1997; Hagenauer et al, 2009). Furthermore, there is a high incidence of sleep disturbance during youth (Gradisar et al, 2011). A delayed sleep phase (DSP) is not considered a diagnosis, but is associated with negative consequences such as lower grades, school absence, smoking, alcohol use, and mental health problems (Saxvig et al, 2012; Sivertsen et al, 2015; Sivertsen, Harvey et al, 2015).

The prevalence of DSP has been estimated at 3.3–8.4% of teenagers aged 16–19 years (Saxvig et al., 2012; Sivertsen, Harvey, et al., 2015) Among the teenagers with DSP, 5.7% had problems advancing the sleep phase and overslept at least 2 days per week or reported much or very much sleepiness at school (Saxvig et al., 2012). Whereas some individuals only develop a DSP, others will fulfill the criteria for the diagnosis of DSPD.

DSPD

DSPD was first described in 1981, and was present in 30 of 450 insomnia patients in the initial report (Weitzman et al., 1981). These persons had difficulty falling asleep and waking up at conventional times. If they were allowed to sleep without external restrictions, they slept for a normal length of time and without pathology in their sleep architecture. This sleep disorder was named delayed sleep phase syndrome and is the most common circadian rhythm sleep-wake phase disorder. In the first version of the International Classification of Sleep Disorders (ICSD) published in 1991 and the subsequent version published in 2001 (ICSD-rev), the disorder was still named Delayed sleep phase syndrome (American Academy of Sleep Medicine, 1991 & 2001). However, in the International Classification of Sleep Disorders, second edition (ICSD-2) published in 2005, the disorder was named Circadian rhythm sleep disorder, delayed sleep type (Delayed sleep phase disorder) (American Academy of Sleep Medicine, 2005). In the latest version of the ICSD (third edition, ICSD-3, published in 2014), the disorder is named Delayed sleep-wake phase disorder (American Academy of Sleep Medicine, 2014). I used the term delayed sleep phase disorder (DSPD) in this thesis since the participants in paper III, IV and V were diagnosed according to the ICSD-2 criteria.
Diagnosing DSPD

Diagnostic criteria according to ICSD-2

When diagnosing DSPD, both the general criteria for a circadian rhythm sleep disorder (CRSD) and the more specific criteria for DSPD must be fulfilled. The general criteria for all CRSD according to ICSD-2 (American Academy of Sleep Medicine, 2005) are:

- A persistent or recurrent pattern of sleep disturbance due primarily to one of the following:
  - Alteration of the circadian time keeping system
  - Misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.
- The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.
- The sleep disturbances are associated with impairment of social, occupational, or other areas of functioning.

According to ICSD-2 the following criteria must also be met to diagnose DSPD:

- There should be a delay in the phase of the major sleep period in relation to the desired sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a socially acceptable time.
- When allowed to choose their own sleep schedule, they exhibit improved sleep quality and duration for age and maintain a delayed, but stable phase of entrainment to the 24 h sleep-wake pattern.
- Sleep log and, whenever possible, actigraphy monitoring for at least 7 days must demonstrate a delay in the timing of the habitual sleep period.
- The sleep disturbance is not better explained by another current sleep disorder, a medical or neurological disorder, a mental disorder, medication use, or a substance use disorder.

The diagnostic criteria according to DSM-V

The Diagnostic and statistical manual of mental disorder, 5th Ed (DSM-V) (American Psychiatric Association, 2013) have very similar diagnostic criteria as ICSD-2. These criteria were operationalized in paper I.

- A chronic or recurrent pattern of a delayed sleep-wake rhythm primarily due to alteration of the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual’s physical environment or social/work schedules.
- The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.
The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

DSPD can be classified as episodic (1–3 months duration of symptoms) or persistent (more than 3 months duration of symptoms). If two or more episodes occur during 1 year, it can be classified as recurrent.

**Earlier and more recent versions of diagnostic criteria for DSPD**

The criteria for DSPD have changed over the years (American Academy of Sleep Medicine, 1991 & 2001).

Older criteria from the first ICSD and ICSD-Rev have included:

1) A sleep-wake log maintained for at least 2 weeks should demonstrate a delay in the habitual sleep period.

2) The DSPD symptoms should have been evident for at least 1 month.

3) One of the following laboratory methods must demonstrate a delay in the timing of the habitual sleep period:
   - (a) 24 h polysomnography monitoring (or two consecutive nights with polysomnography and an intervening multiple sleep latency test).
   - (b) Continuous temperature monitoring showing that the time of the absolute temperature nadir is delayed into the second half of the habitual (delayed) sleep episode.

The criteria in ICSD-2 are very similar to those in ICSD-3. The big difference is that in ICSD-3 the symptoms of DSPD must have been evident for at least 3 month.

There are no criteria that require laboratory methods to demonstrate a delay in the timing of the habitual sleep period in the 2 latest versions of ICSD (American Academy of Sleep Medicine, 2005 & 2014). However, it is noted that measurements of dim light melatonin onset (DLMO) or acrophase of 6-sulphatoxymelatonin is desirable. Furthermore standardized chronotype questionnaires are recommended to assess the chronotype of eveningness and morningness. Individuals with DSPD typically score as evening types. In ICSD-3, the Horne Östberg Morningness-Eveningness Questionnaire and the Munich Chronotype Questionnaire are mentioned as useful tools for accessing chronotype in DSPD.

**Assessing circadian phase in DSPD**

Human circadian rhythms can be measured through core body temperature, plasma or saliva melatonin, and urine 6-sulphatoxymelatonin. DLMO or acrophase of melatonin are desirable to confirm the delay in circadian rhythm, as noted in both ICSD-2 and ICSD-3(American Academy of Sleep Medicine, 2005 & 2014). Studies on young individuals show clear correlations between DLMO and sleep timing (Burgess & Eastman, 2005; Burgess et al., 2003; Crowley et al., 2006). It has been suggested that self-reported
sleep times from sleep logs are sufficient to estimate DLMO in young adults (Martin & Eastman, 2002) however, there is considerable inter-individual variability in the phase angle between DLMO and habitual sleep times in healthy adults (Sletten et al, 2010; Wright et al, 2005). Melatonin concentrations measured in urine, saliva, and plasma are comparable, and there are significant correlations between serum and salivary melatonin concentrations \((r = 0.81, p < 0.001)\) and between serum melatonin concentration and 6-hydroxymelatonin sulfate excretion rate in urine \((r = 0.72, p < 0.001)\) (Nowak, McMillen, Redman, & Short, 1987).

**Core body temperature**

Core body temperature is best obtained by gut or rectal temperature monitoring and should be measured for at least 24 h to obtain the nadir of the core body temperature. The nadir of core body temperature has a strong relation to the melatonin curve. However, melatonin is a more stable marker of circadian phase when measured under constant routine conditions (Benloucif et al., 2005)

**6-sulphatoxymelatonin in urine**

6-sulphatoxymelatonin is a metabolite of melatonin. It can be collected in urine every 2–8 h over a 24 to 48 h period and is a practical method to estimate the global timing and amount of melatonin production. This is often used to estimate the timing of the acrophase (time of fitted peak) of a cosine fitted curve (Benloucif et al., 2008).

**Melatonin in plasma and saliva**

Melatonin can also be measured directly in plasma and saliva. Plasma melatonin level is about three times higher than saliva melatonin level. The higher melatonin level present in plasma allows greater resolution and sensitivity than is obtained when sampling urine or saliva, and is particularly useful for individuals with low melatonin concentrations. However, in general, saliva melatonin is seen as the more practical approach as it is noninvasive (Benloucif et al., 2008). Melatonin samples should be obtained during dim light conditions (<15lux) so the melatonin secretion is not affected by light (Pandi-Perumal et al., 2007). When measuring melatonin in plasma or saliva, it is possible to separately determine DLMO, acrophase of melatonin, and dim light melatonin offset. DLMO is the most commonly used measure of circadian rhythm.

There are different approaches to quantifying DLMO. Examples of these approaches are visual inspection of a change in the slope, threshold crossing (i.e., identifying when the melatonin level reaches a certain threshold: absolute [most frequently ranging from 2 to 10 pg/mL], relative to baseline, or a percentage of maximum), and the fit of a cosine curve (Pandi-Perumal et al., 2007).
Laboratory analysis of melatonin
The volume of saliva needed to measure melatonin is at least 0.4 mL per tube, or 1 mL for duplicates. Saliva samples are often collected by chewing on a swab and should be kept constantly on ice and protected from light radiation to avoid degradation. Immunochemistry-based methods such as radioimmunoassay and enzyme-linked immunosorbent assay are most frequently used to measure melatonin in the laboratory. There is a potential risk of cross-reactivity from structurally similar compounds when applying these methods. In the last few years, several mass spectrometry-based techniques have become increasingly popular. There are also potential analytical problems in these methods, such as matrix effect and ion suppression (Jensen et al, 2014)

Prevalence of DSPD
The prevalence of DSPD is uncertain, and is reported as between 1% and 10% in adolescents (Lovato et al, 2013; Sivertsen et al., 2013; American Academy of Sleep Medicine, 2014). Only a few studies have studied participants spanning a large age range. In one of these studies, the prevalence of DSPD was estimated as 0.17% in adults aged 18–67 years, and 0.34% in young adults aged 18–19 years (Schrader et al, 1993). In this study, the authors also looked at a separate condition of motivated sleep phase delay, and estimated the prevalence as 4.6% young adults aged 18-19 years. However, a more recent study estimated the prevalence of DSPD sleep disorder at 1.5–8.9%, depending on the criteria used to diagnose the sleep disorder (Paine et al, 2014). A recent study using sleep diaries and wrist actigraphy reported a prevalence of DSPD of 1.1% in teenagers (Lovato et al, 2013).

According to some clinical data, boys are over-represented among persons with DSPD (Thorpy et al, 1988). However, the studies mentioned above showed no gender differences in the prevalence of DSPD, although men were over-represented among persons with motivated sleep phase delay. Furthermore, a recent Norwegian study reported a prevalence of DSPD of 3.3% in teenagers aged 16–18 years, and demonstrated an over-representation of girls in this group (Sivertsen et al., 2013). This study reported a higher frequency of school truancy among the boys with DSPD than among girls with DSPD.

Social impairment and psychiatric comorbidities observed in DSPD
DSPD is associated with both social impairment and psychiatric comorbidities. An extreme DSP often leads to missing classes at school or arriving late at work. If persons with DSPD do manage to get up in the morning, they are extremely tired and sleepy during the day. Often, persons with DSPD are
accused of being lazy, uninterested, unengaged, and unwilling to follow society’s demands and expectations. Poorer academic performance is associated with both DSPD and DSP, and is thought to be caused by a combination of school absence and short sleep duration (Gradisar & Crowley, 2013). Common symptoms associated with DSPD are irritability, poor concentration, and memory problems. Persons with DSPD often have psychiatric disorders such as depression, anxiety (especially obsessive-compulsive disorder), attention deficit/hyperactivity disorder, and substance abuse (Dagan et al, 1998; Kooij & Bijlenga, 2013; Lange et al, 2012; Reid et al, 2012; Schubert & Coles, 2013). A recent study demonstrated a high overlap between insomnia and DSPD; about 50% of participants with DSPD also fulfilled the criteria for insomnia (Sivertsen et al, 2013). Polymorphisms in genes associated with bipolar disorder and attention deficit/hyperactivity disorder have also been associated with DSPD (Archer et al., 2010).

Pathogenesis of DSPD

The pathogenesis of DSPD is not yet completely understood. Alterations in the circadian clock and changes in homeostatic regulation of sleep both play a role in the onset of DSPD in adolescents.

A delay of the circadian clock is probably the most established hypothesis regarding the pathogenesis of DSPD. A 2–6 h delay in DLMO, a delay in the occurrence of minimum core body temperature, and a delay in the melatonin peak have all been observed in persons with DSPD.

The time between the core body temperature minimum and sleep offset is longer in DSPD patients than in controls (Ozaki et al,1996; Uchiyama et al, 2000). This may mean that persons with DSPD are sleeping when light exposure would be as most effective to advance the melatonin rhythm. However, a more recent study has not confirmed these findings (Chang et al, 2009).

A long circadian period may also be involved in the pathogenesis of DSPD (Micic et al., 2013). A recent study reported a circadian period of 24h and 52 minutes in persons with DSPD (Micic et al., 2013). This means that persons with DSPD have to phase advance almost 60 min each morning, compared to normal sleepers who only have to phase advance 12 min each morning.

Homeostatic sleep drive mechanisms may also be altered in DSPD, and persons with DSPD may accumulate homeostatic sleep drive more slowly during wakefulness compared to controls. Furthermore, persons with DSPD have longer intervals between habitual sleep onset and sleep offset (Uchiyama et al, 1999; Uchiyama et al, 2000).

There is also evidence that persons with DSPD are more sensitive to light during the evening than persons without DSPD (Aoki et al, 2001; Archer et al., 2010; Cain et al., 2013). This increased light sensitivity may be driven by hormonal changes (androgens and estrogens) during puberty. Animal studies demonstrated that gonadal hormones can modulate photic sensitivity, either
through alterations in the glutamatergic signaling from the retinohypothalamic tract or by modulating the indirect pathways to the SCN (Hagenauer & Lee, 2012).

It is probable that these possible contributors to DSPD have a genetic basis. Polymorphisms in hPER3 genes are the genotypic difference predominantly related to the circadian period. The photoperiodic signal of melatonin is decoded via differential phasing of the transcription factors Per and Cry in the pars tuberalis (Messager et al, 1999). DSPD has been associated with polymorphisms in hPER1, hPER2, and hCLOCK, and there is a higher incidence of arylalkylamine N-acetyltransferase and HLA-DR-1 alterations in DSPD than in controls (Archer et al., 2010; Carpen, 2005; Carpen et al, 2006; Hohjoh et al, 1999; Hohjoh et al, 2003). Conversely, mutations of S408N in hCKIepsilon act as protective factors against DSPD (Takano et al., 2004).

Personality profile and psychological aspects of DSPD

Recent studies discuss whether personality and behavioral factors can contribute to DSPD, and the personality profile of persons with DSPD has been assessed in a few studies. Scores on conscientiousness, extraversion, and agreeableness were lower and score on neuroticism was higher in persons with DSPD than in controls (Wilhelmsen-Langeland et al., 2014, Micic et al., 2016). Individuals with more severe DSPD had more extreme personality traits, especially conscientiousness. Persons with a low conscientiousness score tended to be less organized, be less driven, and procrastinate on tasks, and were more prone to quitting (Costa et al., 1992). However, the existence of a causal link between DSPD and these personality traits has not yet been found.

Cognitive processes related to DSPD include sleep-related attentional bias (MacMahon et al, 2006; Marchetti et al, 2006), distorted perception of sleep and daytime functioning and dysfunctional beliefs (Saxvig et al, 2014; Wilhelmsen-Langeland et al, 2013). Physiological pre-sleep arousal might occur when a person with DSPD tries to go to bed at a more socially conventional time and experiences difficulties initiating sleep. It has even been suggested that DSPD can cause conditioned insomnia, and vice versa. Moreover, behavioral factors, such as decreased exposure to light during the morning (due to late sleep offset) and prolonged exposure to light late in the evening, may contribute to the delayed sleep pattern.

Treatment of DSPD

The most commonly recommended treatment regimens for DSPD are bright light exposure in the morning or melatonin in the evening (Morgenthaler et al., 2007). The timing of these treatments is crucial, as an inappropriate time of administration can worsen the DSPD. Chronotherapy (the delay of sleep
and wake times every day until the desired sleep and wake times are achieved) can be used in the treatment of DSPD, but the efficacy is less documented than for LT and melatonin, and there have been no controlled trials (Morgenthaler et al., 2007).

**Exogenous melatonin**

Melatonin in the evening (before the temperature minimum) advances the phase of the circadian clock (Mundey et al, 2005; Nagtegaal et al, 1998). There is one long-term study of melatonin for the treatment of delayed sleep-wake phase disorder (Dagan et al, 1998). In this study, there was a very high frequency of relapses. Known side effects of melatonin are elevation of blood pressure, headache, dizziness, nausea, and drowsiness (Buscemi et al, 2005). Furthermore, melatonin is involved in the seasonal regulation of animals’ reproduction (Srinivasan et al, 2009), and there are some concerns about its long-term use during childhood and adolescence. There are still too few studies in humans on long-term treatment with melatonin and its side effects.

Melatonin in the evening and LT for 30 min 12 h later was better than no treatment in maintaining an advanced sleep onset and offset. (Saxvig et al, 2014; Wilhelmsen-Langeland et al, 2013). Furthermore, fatigue, daytime sleepiness, and cognitive performance were better after this treatment than after no treatment.

**Light therapy (LT)**

Light is the main synchronizer of the SCN. Bright white light over 2500 lux can suppress melatonin completely (Lewy et al, 1980), but domestic intensity light also significantly suppresses the production and release of melatonin (Bojkowski et al, 1987; Zietzer et al., 2000b). Light also directly influences the expression of the clock gene feedback loops driving circadian rhythms (Reppert, 2000). Furthermore, in addition to the indirect effect of light on sleep through shifting the phase of circadian rhythms, recent findings highlight the importance of the direct effects of light on sleep and alertness (Cajochen et al, 2000; Hubbard et al, 2013; Tsai et al., 2009), cognition (Vandewalle et al, 2009), and mood (Stephenson et al, 2012). Additionally, light affects the sleep homeostatic process (Tsai et al, 2009), which is another way to modulate sleep regulation.

**Wavelength**

There is a dose-response relation between light and its effects. Light of 9500 lux induced a larger phase shift in the temperature nadir than light of 180 lux (Boivin et al, 1996). The timing of light exposure was 1.5 h after the minimum core body temperature. When melanopsin-containing ganglion cells in the eye were discovered, it was observed that light with a shorter wavelength (446-477 nm) produced the highest melatonin suppressive effect and largest delay in DLMO (Brainard et al., 2001). Since this discovery, a lot of focus
has been placed on blue or blue-enriched white light. Nevertheless, white light is most commonly used in LT. This is due to inconsistent data concerning the safety of blue light on the retina and the lens, in addition to a lack of clinical guidelines.

**Duration**
There are studies that have focused on duration of LT as the most important factor for the phase advance, whereby longer durations produce larger phase shifts (Dewan et al, 2011). However, Chang et al. concluded that short exposure to bright light was more efficient than long exposure for phase shifting, suppressing melatonin, and inducing alertness (Chang et al, 2012). Clinical recommendations are 30 min exposure to bright light (Bjorvatn & Pallesen, 2009), and a recent study confirmed these recommendations, showing that 30 min of LT with 5000 lux produced 75% of the phase shift observed after 2 h of LT with 5000 lux (Crowley & Eastman, 2015).

**Timing**
The timing of light exposure during the day has a crucial role in the phase-shifting effects of light. For the largest advance in phase, exposure to light should be directly after the minimum core body temperature during the night (Khalsa et al, 2003; Minors et al, 1991). However, it is difficult to achieve this timing. Different suggestions have been made on when in the morning to start LT. The easiest ways is to start light exposure directly after natural awakening and then start to advance wake-up time by half an hour each day. If LT is combined with melatonin, light should be administered 12 h after melatonin intake. If the time of DLMO is known, LT has been recommended about 8–9 h after DLMO (Terman & Terman, 2005).

**Side effects and contraindications**
Irritability, headache, nausea, and eye irritability are common side effects of LT and are easily resolved by a simple reduction in light intensity. Light in the ultraviolet spectra is never used in LT devices because of the potential phototoxic effects on the lens and retina. Caution should be taken if considering LT for persons with bipolar disorder, existing ocular pathogenesis, or photosensitive skin, or taking photosensitizing medications (Kogan & Guilford, 1998; Terman & Terman, 2005).

**Treatment studies with LT**
In a randomized controlled trial, a fixed sleep schedule for 6 days with no LT was just as effective in phase advancing DLMO, bed time, and rise time as a fixed sleep schedule with blue (470 nm) light in the morning (Sharkey et al, 2011). In another randomized controlled trial of a 2700 lux illuminated mask compared to a placebo mask, persons with a more severe delay in DLMO had significantly better results (Cole et al, 2002). LT with 2500 lux
light for 2 h each morning in combination with wearing dark goggles after 16:00 h resulted in a significantly greater phase advance of the temperature nadir and greater improvements in multiple sleep latency tests than LT with placebo light (300 lux) in DSPD patients (Rosenthal et al., 1990).

Cognitive Behavior Therapy (CBT)

CBT has been suggested as a possible additive treatment in DSPD. Relapses are common after both melatonin treatment and combination therapies with melatonin and LT (Alvarez et al., 1992; Dagan, Yovel, et al., 1998; Saxvig et al., 2014; van Maanen et al, 2011), and it is very likely that cognitive processes such as: pre-sleep arousal, sleep-related attentional bias, distorted perception of sleep and daytime functioning, dysfunctional beliefs and safety behaviors are involved in the development and maintenance of DSPD (Richardson et al, 2016). Additionally it has been noted from clinical experience (Lack & Wright, 2007) that cognitive and behavioral factors might exacerbate DSWPD. Such factors include choosing to delay bedtime resulting in later awakenings, frustration and anxiety when trying to advance bedtime with lengthened sleep latency as a result, the bedroom acting as a trigger eliciting conditioned arousal, trying to resume sleep in the morning following forced early awakenings, and avoidance of early awakenings due to previous aversive experiences. Furthermore the overlap between DSWPD and insomnia is large (Sivertsen et al., 2013), particularly when patients attempt to sleep at earlier times. Thus, it is possible that interventions that target insomnia symptomatology, such as CBT (Morin et al., 2006) might have an impact on insomnia and possible also the delayed sleep in those with DSWPD.

One randomized controlled trial have shown that CBT together with bright light resulted in moderate-to-large improvements in sleep latency, sleep onset, rise times, total sleep time, wake after sleep onset, sleepiness, and fatigue (Gradisar, Dohnt, et al., 2011). However, the design of this study means that it is not possible to tease out the effects of CBT alone, i.e., without LT.
Aims and scope

DSPD is a relatively new and probably underdiagnosed sleep disorder, which can cause significant social and functional impairment. There are treatment recommendations for DSPD, but clinical trials are still sparse. The overall aim of this thesis was to evaluate at-home treatment with Light therapy (LT) and the feasibility of adding cognitive behavior therapy (CBT) to LT in DSPD, furthermore prevalence, diagnostic aspects and associated factors were investigated.

The specific aims of this thesis were:

• to estimate the prevalence of DSPD and DSP in a Swedish cohort of adolescents and young adults and to investigate factors associated with DSPD and DSP.

• to investigate the association between DLMO and the sleep-wake rhythm and diurnal preference in healthy working adults in real-life conditions.

• to evaluate the feasibility of CBT as an additive treatment to LT for DSPD and determine whether CBT enhanced and preserved the treatment response to LT.

• to assess the effect of LT with scheduled rise times on sleep-wake rhythm and identify predictors of this effect.
Method

Study design
An overview of the study designs is presented in Table 1.

Participants
The demographics of the study participants are presented in Table 2. Participants in study I were teenagers and young adults aged 16–26 years old living in Uppsala. Participants were randomly selected by the Swedish Population Register.

Participants in study II were healthy working adults. Exclusion criteria for study II were shift work, score > 10 on the Epworth Sleepiness Scale (ESS), and score > 7 on the Minimal Insomnia Symptom Scale (MISS).

Participants in studies III, IV, and V were aged 16–26 years and fulfilled the criteria for DSPD according to ICSD-2 (American Academy of Sleep Medicine, 2005). The criteria for DSPD were operationalized as follows: a) A mean sleep onset later than 01:00 AM in their 7 day sleep diary. b) Late sleep offset and great difficulties rising in the morning indicating a delay in the major sleep episode. c) If allowed to choose their own sleep-wake rhythm, they exhibited improved sleep quality and duration for age and maintained a delayed phase of the 24-hour sleep-wake pattern. d) Participants exhibited either insomnia symptoms or daytime sleepiness because of their delayed sleep-wake rhythm. e) The sleep disorder should also have caused distress or dysfunction. f) The sleep disturbance was not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Exclusion criteria for studies III, IV, and V were any eye disease, and medicating with substances that can affect sleep patterns or interact with light.

Participants were recruited to the treatment study through advertisements in the local newspaper and student magazines. A brief phone screen and information about the study were given to those who responded to the advertisement (n=122). Eighty-six individuals were invited to the Sleep Centre to enrol in the study, and 63 participants attended this visit. Fifty-seven participants were eligible for the study. The participant flowchart for studies III, IV, and V is shown in Figure 2.
Table 1. An overview of the studies included in this thesis

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
<th>Study V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Cohort study</td>
<td>Observational study</td>
<td>Randomized controlled trial investigating LT+CBT versus LT+NT</td>
<td>Manual description of the CBT</td>
</tr>
<tr>
<td>Recruitment method</td>
<td>The Swedish Population Register</td>
<td>Convenience sample</td>
<td>Advertisement</td>
<td>Advertisement</td>
</tr>
<tr>
<td>Number of participants</td>
<td>671</td>
<td>14</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Prevalence of and factors associated with DSPD and DSP</td>
<td>DLMO and sleep-wake rhythm</td>
<td>Sleep-wake rhythm, insomnia, daytime sleepiness, and anxiety and depressive symptoms</td>
<td>The reception of the CBT program</td>
</tr>
<tr>
<td>Follow-up</td>
<td>None</td>
<td>None</td>
<td>2 weeks, 6 weeks, and 6 months</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>t-test, chi-square, and logistic regression</td>
<td>Spearman’s rank correlation coefficient</td>
<td>Mixed model</td>
<td>None</td>
</tr>
</tbody>
</table>

CBT, cognitive behavioral therapy; DSP, delayed sleep phase; DSPD, delayed sleep phase disorder; LT, light therapy; NT, no treatment
Table 2. Characteristics of the participants in each study

|                              | Study I  
<table>
<thead>
<tr>
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<th></th>
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<tr>
<td></td>
<td>N = 671</td>
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<tr>
<td>Female</td>
<td>55.3%</td>
</tr>
<tr>
<td>Age, years</td>
<td>21.77 ± 3.1</td>
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<tr>
<td>Work or educational activity</td>
<td>94.5%</td>
</tr>
<tr>
<td>Residential status (living alone)</td>
<td>28%</td>
</tr>
<tr>
<td>DSPD</td>
<td>4%</td>
</tr>
<tr>
<td>DSP not fulfilling criteria for DSPD</td>
<td>4.6%</td>
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<tr>
<td>Non-DSP</td>
<td>91.6%</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Study II N = 17</th>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>41%</td>
</tr>
<tr>
<td>Age, years</td>
<td>44 ± 1.3</td>
</tr>
<tr>
<td>Work or educational activity</td>
<td>100%</td>
</tr>
<tr>
<td>Residential status (living alone)</td>
<td>0%</td>
</tr>
<tr>
<td>DSPD</td>
<td>0%</td>
</tr>
<tr>
<td>DSP not fulfilling criteria for DSPD</td>
<td>0%</td>
</tr>
<tr>
<td>Non-DSP</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Studies III and IV N = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>47%</td>
</tr>
<tr>
<td>Age, years</td>
<td>21.77 ± 2.73</td>
</tr>
<tr>
<td>Work or educational activity</td>
<td>89%</td>
</tr>
<tr>
<td>Residential status (living alone)</td>
<td>52.8%</td>
</tr>
<tr>
<td>DSPD</td>
<td>100%</td>
</tr>
<tr>
<td>DSP not fulfilling criteria for DSPD</td>
<td>0%</td>
</tr>
<tr>
<td>Non-DSP</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Study V N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>50%</td>
</tr>
<tr>
<td>Age, years</td>
<td>21.77 ± 2.73</td>
</tr>
<tr>
<td>Work or educational activity</td>
<td>79%</td>
</tr>
<tr>
<td>Residential status (living alone)</td>
<td>52.3%</td>
</tr>
<tr>
<td>DSPD</td>
<td>100%</td>
</tr>
<tr>
<td>DSP not fulfilling criteria for DSPD</td>
<td>0%</td>
</tr>
<tr>
<td>Non-DSP</td>
<td>0%</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or percent. DSP, delayed sleep phase; DSPD, delayed sleep phase disorder

Protocol failures in study III, IV and V

Protocol failures were those participants that (a) were randomized to a group but never started the intervention (LT or CBT), (b) fulfilled any of the exclusion criteria during the study, or (c) started an adjunct therapy that could influence the results. During LT, nine participants never used the LT lamp (Figure 1) and two participants in the LT and no further treatment (LT+NT) group experienced side effects from the LT lamp (headache and feeling over-excited) and did not want to continue LT. In the second phase of the study, three participants in the LT+CBT group did not attend CBT sessions because of lack of time. One participant in the LT+CBT group expressed suicidal thoughts and plans about hurting himself and was withdrawn from the study at week 3 and referred to the acute psychiatric department. One participant in the LT+CBT group started using antidepressants and one participant in the LT+NT group started using sleep medication before the week 6 assessment. Before the 6 month follow-up assessment, one participant from each group (LT+NT and LT+CBT) started therapy in the psychiatric clinic and one from each group (LT+NT and LT+CBT) started using sleep medication.

Independent sample t-tests showed no significant differences in sleep onset, sleep offset, sleep duration, sleep quality, daytime sleepiness, anxiety, depression, or birth year between protocol failures and participants who continued in the study. In study III, protocol failures (n = 20) had a significantly higher score for severity of sleep difficulties (mean± standard deviation (SD)
were 17.25 ± 3.16) than participants who continued in the study (n = 37, 15.04 ± 3.16; p = 0.04). In study V, the only significant difference between completers (n = 44) and protocol failures (n = 13) was that completers had a more pronounced eveningness chronotype measured with the Horne Östberg morningness eveningness questionnaire (29.72 ± 4.06) than dropouts (37± 6.27, p < 0.01).

Figure 2. The participant flowchart for studies III, IV, and V
DSP and DSPD criteria in study I

The DSM-V provides four criteria that should be met for the proper diagnosis of DSPD: 

(A) a delay in the major sleep episode, 

(B) excessive daytime sleepiness or insomnia caused by the sleep disorder and 

(C) significant daytime impairment or distress due to the sleep disorder. To specify the disorder as chronic there should be evidence of the sleep disorder for at least 3 months. DSP was defined as a delay in the major sleep episode (Criterion A) without fulfillment or only partial fulfillment of the other three criteria.

   Criterion A was defined as falling asleep after 01:00 h at least 3 days per week and having a preferred wake up after 09:45 h, if possible. The first question in the reduced Horne Östberg Morningness-Eveningness Questionnaire (rMEQ) addresses the preferred wake-up time.

   Criterion B was operationalized as moderate-to-severe difficulty in falling asleep (≥2 points on the first question in the Insomnia Severity Index [ISI]) or excessive daytime sleepiness (≥10 points on the ESS).

   Criterion C was defined as ≥2 points on question 5 of the ISI (ranging from somewhat interference to very much interference with daytime functioning due to the current sleep disturbance) or ≥2 points on question 7 of the ISI (ranging from somewhat worry to very much worry about the sleep disturbance).

The specification of the sleep disorder was operationalized as the presence of a sleep disturbance for at least 3 months.

Ethics

In studies II, III, IV, and V, all participants provided oral and written informed consent, and anonymity was preserved throughout the study. The Regional Ethical Vetting Board in Uppsala, Sweden approved the study protocols. In study I, participants did not receive any compensation. In studies III, IV and V, participants received compensation for expenses for travel to the Sleep Centre.

For study I, an advisory statement concerning research involving humans was received from the Regional Ethical Vetting Board, Uppsala, Sweden. In the information sent to participants, they were informed that their answers would be included in a study and that they would be completely anonymous. Those who sent back a completed questionnaire received two cinema tickets.

Measures

Dim Light Melatonin Onset (DLMO)

DLMO was measured in saliva in all participants in studies II, III, IV, and V. In study II, participants arrived at the Sleep Medicine Unit at 18:30 h and
saliva samples were collected every 30 min from 19:00 to 23:00 h. In studies III, IV, and V, time of DLMO was measured at the initial visit. Saliva samples were taken hourly between 22:00 and 01:00 h or between 23:00 and 02:00 h, depending on the sleep pattern reported in the sleep diary.

The DLMO test was conducted according to a previously described protocol (Pandi-Perumal et al., 2007). Participants were placed in a dimly lit room (<15 lux) 30 min prior to sampling to prevent suppression of melatonin secretion by bright light. Saliva samples were collected by gently chewing on a cotton swab (Sarstedt Salivette) for approximately 2 min. A small snack and something to drink were allowed immediately after each collection, and participants rinsed their mouth 15 min prior to the next collection.

In study II, tubes containing saliva samples were stored overnight in a refrigerator at +4°C and then transported to the Clinical Chemistry Laboratory at the Uppsala University Hospital for centrifugation. The samples were kept frozen at -20°C until analysis (Direct Saliva Melatonin ELISA, Bühlmann, Switzerland). In study II, DLMO was defined as the time at which melatonin level reached 3 ng/L (Benloucif et al., 2008). In studies III, IV, and V, DLMO was defined as the time at which melatonin level reached 4 ng/L (Rahman et al, 2009).

Questionnaires

Sleep diary
A 7-day sleep diary was kept prior to the first visit in studies II, III, IV and V, and during the 2 weeks of LT, after the final CBT session (week 6 assessment), and 6 months after the start of LT (follow-up assessment) in the treatment studies. The sleep diary was used to quantify time of sleep onset, time of sleep offset, sleep duration, and sleep quality. In study III, sleep quality was rated on a numerical scale ranging from one to five (1 = very poor, 5 = very good). During LT, participants also recorded each day they used the lamp, and what time of day and for what duration they used the lamp. In study III, the sleep diary was also used to measure remission in sleep onset (falling asleep before 01:00 h) and sleep offset (waking up before 09:00 h). In study V, the sleep diary was also used to quantify adherence to the LT schedule (rising at 09:00 h or earlier and use of LT) and remission (falling asleep before 01:00 h and waking up before 09:00 h).

Insomnia
In studies III and V, sleep difficulties were assessed using the ISI. The ISI is a standardized measure of sleep disturbance with established psychometric properties (Bastien et al, 2001). It is a seven-item scale that assesses seven insomnia domains: severity of initial insomnia, middle insomnia and late insomnia, sleep satisfaction, interference of insomnia with daytime functioning, noticeability of sleep problems by others, and distress about sleep difficulties. Each item is scored on a five-point Likert scale, and the
total score ranges from 0 to 28, with higher scores indicating more severe sleep difficulties. The ISI has acceptable psychometric properties in insomnia patients (Bastien et al., 2001).

This is the first study to use the ISI in persons with DSPD; therefore, psychometric analyses were performed on the baseline data in study III. The mean score for each of the seven items differed as expected: item 1, $M = 2.9$ ($SD = 1.0$); item 2, $M = 1.1$ ($SD = 1.2$); item 3, $M = 0.7$ ($SD = 1.2$); item 4, $M = 3.4$ ($SD = 0.6$); item 5, $M = 3.1$ ($SD = 0.7$); item 6, $M = 2.2$ ($SD = 1.0$); item 7, $M = 2.3$ ($SD = 1.0$). The severity of middle and late insomnia was less than that of initial insomnia ($p = 0.001$). There were moderate-to-strong correlations between the total ISI score and score on each of the seven items ($r = 0.48–0.68$), and the internal consistency was acceptable ($\alpha = 0.70$).

In study V, items 4 and 6 from the ISI were used to measure daytime functioning. In studies III and IV the ISI was used to measure sleep difficulties. Remission in sleep difficulties was defined as an ISI score below 8.

In study II, all participants completed the MISS. This is a three-item questionnaire, where higher scores indicate more insomnia symptoms. A MISS score < 7 indicates no insomnia problems (Broman et al, 2008). All participants in study II had a MISS score < 7.

**Daytime sleepiness**
The ESS was used to evaluate daytime sleepiness. This is a symptom scale (Johns, 1991) that has previously been used to evaluate daytime sleepiness in several patient groups, including DSPD (Wyatt et al, 2006). It is an eight-item scale that assesses the risk of falling asleep in different situations during the day. Each item is scored on a four-point Likert scale, and the total score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness. This questionnaire was used to evaluate daytime sleepiness in studies I, II, III, IV, and V.

**Depression and anxiety**
The Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression (Zigmond & Snaith, 1983). The scale consists of a subscale for anxiety (HADS-A) and a subscale for depression (HADS-D). Each subscale consists of seven items that are scored on a four-point Likert scale. The total score for each subscale ranges from 0 to 21, with higher scores indicating greater anxiety or depression. A score $\geq 8$ is considered as possible anxiety or depression. This questionnaire was used in studies I, III, IV, and V.

**Morningness-Eveningness**
The Morning-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976) is a standard measure of diurnal preference and contains 19 items. The MEQ was used in studies II and V. The alternative scoring proposed by Taillard et
al. (2004) was used in study II (Taillard et al., 2004), and the original scoring was used in study V.

In study I, the degree of eveningness chronotype was evaluated using the reduced MEQ (rMEQ) (Adan & Almira Ilı, 1991). The rMEQ contains questions 1, 7, 10, 18, and 19 from the MEQ. The total score ranges from 4 to 25 points. A lower score indicates a diurnal preference for the evening.

Credibility and expectancy
To evaluate the perceived credibility and expectancy of the CBT intervention, the Credibility/Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000) was administered at the end of the first CBT session in studies III and IV. Scores on the CEQ can range from one to nine.

Worry
The Penn State Worry Questionnaire (PSWQ) was used to evaluate worry in study V. This is a 16-item scale, and each item is scored on a five-point Likert scale. The total score ranges from 16 to 80, with higher scores indicating a higher level of worry (Meyer et al., 1990). In study V, the three-item PSWQ was used to evaluate worry (Berle et al., 2011). This questionnaire contains questions 4, 14, and 15 from the PSWQ, and each item is scored on a five-point Likert scale. The total score therefore ranges from 3 to 15, with higher scores indicating a higher level of worry.

Rumination
The Symptom-Focused Rumination Scale (SRS) was used to evaluate rumination (Bagby & Parker, 2001). This is an eight-item scale, and the total score ranges from 8 to 32, with higher scores indicating a higher level of rumination.

Interventions
Light therapy (LT)
All participants in studies III, IV, and V received 2 weeks of LT. Salivary measures of DLMO were made at the initial visit. Before LT started, participants received information on their melatonin curve and why their LT was scheduled at a certain time in the morning, and were informed that light later in the day or in the evening might worsen their delay in sleep phase.

Participants were instructed to undergo LT at home for 30–45 min per day (Bjorvatn & Pallesen, 2009) for 14 days using 10 000 lux white bright light (EnergyLigth HF3319/01, Philips). The dimension of the illuminated part of the light box was 48 cm high and 33 cm wide. The fluorescent light tubes in the light box were 2 PL-L 36 W Philips EnergyLight with a color temperature of 3500K. Participants were instructed to after awakening get
out of bed and place themselves at a table when performing LT. They were also instructed to locate themselves 0.5 m from the lamp, and encouraged to have breakfast while using the LT lamp.

During the 2 weeks of LT, participants kept a sleep diary. To quantify LT compliance, participants also recorded for how long and at what times they used the LT lamp each day. LT treatment began between September 2011 and March 2012.

Scheduled rise times

During LT, rise time was scheduled 8–8.5 h after DLMO (Terman & Terman, 2005). Most participants could start directly on that schedule. However, four participants had a sleep offset around 12:00 h and should have started to rise around 08:00 h, according to their DLMO. These participants were allowed to use the first 3–4 days of LT to advance sleep offset by 1 h per day. This is according to our clinical routine at the Sleep Centre. Furthermore, several studies showed the efficiency of gradually advancing rise time by 1 h per day (Burgess et al, 2003; Revel et al, 2006; Smith et al, 2009). For the participants in whom DLMO was not obtained, mean sleep offset from the sleep diary was used to determine scheduled rise time at the start of LT. Sleep offset was advanced by 1 h per day.

During the second week of LT, it was recommended that participants use the LT lamp at 09:00 h or earlier. Participants were instructed to use the LT lamp as soon as possible after they had risen from bed.

There were no significant differences in sleep onset, sleep offset, remission, adherence, or daytime functioning between the group that had their LT scheduled according to DLMO and those who had it scheduled according to their sleep diary (calculated using t-test and chi-square test).

Cognitive Behavior Therapy (CBT)

Participants in the LT+CBT group received one group session of CBT per week for 4 weeks after the end of LT. Each session involved between three and six participants and was 90–120 min long. All sessions were held in the afternoon, and followed the same format: a summary of the last session, homework, learning new skills, a summary of the session, and assignment of homework (Figure 2). A licensed psychologist specialized in CBT for insomnia, Markus Jansson-Fröjmark, administered all CBT sessions.

CBT was based on the idea of a transdiagnostic sleep intervention (Harvey, 2009), but with a particular focus on DSPD and notions about how CBT might be implemented for DSPD (Lack & Wright, 2007). The CBT intervention consisted of psycho-education, presenting a CBT-model for DSPD, case formulation, motivational interviewing, registering sleep in a diary, strategies to improve the rhythm of sleep and wakefulness, relaxation training, cognitive restructuring, strategies to cope with daytime symptoms, construct-
ing an individualized CBT program and learning how to deal with relapses, The content of each of the four sessions is shown in Table 3.

Table 3. The content of each of the four CBT sessions

<table>
<thead>
<tr>
<th>Session</th>
<th>Content</th>
</tr>
</thead>
</table>
| 1       | Providing information on sleep, CBT, and DSPD.  
         | Presenting and individualizing a CBT model for DSPD, including possible vulnerability factors and life or environmental circumstances as triggers and maintaining factors, and thoughts and behaviors as maintaining factors.  
         | Underscoring the possibility that applying new, alternative behaviors and thoughts might improve DSPD symptomatology.  
         | Articulating and modifying expectancies.  
         | Using brief motivational interviews to enhance compliance with CBT.  
         | Administering homework assignments: case formulation and sleep diary. |
| 2       | Introducing gradual sleep regulation (15 min advance per day) to go to bed earlier and get up from bed earlier, while still not producing significantly longer sleep onset latency.  
         | Establishing a baseline (via a sleep diary) for sleep regulation and preferred time for “lights out” and rise time.  
         | Introducing stimulus control procedures: being physically active, avoiding naps, avoiding caffeine and nicotine late in the evening, avoiding consuming alcohol on a regular basis, avoiding strenuous mental or physical activity during the last hour of wakefulness, avoiding going to bed too hungry or full, avoiding consuming large amounts of liquid late in the evening, minimizing noise and light exposure, setting the bedroom temperature between 17 and 20°C, going to bed only when sleepy (only administered to participants with long sleep onset latencies), getting up from bed if not able to fall asleep within 15 min after “lights out” and return to bed when sleepy (only administered to participants with long sleep onset latencies), using the bedroom only for sleep and sexual activity, and increasing light exposure during the morning.  
         | Administering homework assignments: sleep regulation, stimulus control procedures, and sleep diary. |
| 3       | Introducing and practicing progressive muscle relaxation training.  
         | Introducing cognitive restructuring, identifying negative automatic thoughts related to DSPD symptomatology. |
refuting the thoughts with Socratic questions, and writing down realistic, credible, less-negative thoughts.

- Reviewing and revising sleep regulation and stimulus control procedures.
- Administering homework assignments: sleep regulation, stimulus control, relaxation, cognitive restructuring, and sleep diary.

4

- Summarizing and rehearsing components of CBT.
- Reviewing improvements in symptomatology.
- Constructing an individualized coping program.
- Learning how to deal with relapses.

CBT, cognitive behavior therapy; DSPD, delayed sleep phase disorder.

Statistics

Statistical analysis was conducted using SPSS version 17.0 in study II and SPSS version 21.0 in all other studies (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± SD, in all studies, and also as median and range in study II. A p value < 0.05 in a two-tailed test was used as the criterion for statistical significance.

Dichotomized demographic and sleep data were compared using a chi-square test in studies I and III and McNemar’s test in study V. Binary logistic regressions were conducted to investigate associations and account for potential covariance in studies I and V. In study I, the dependent variables were participants without DSP vs. participants with DSP but without DSPD, participants without DSP vs. participants with DSPD, and participants with DSP without DSPD vs. participants with DSPD. The independent variables were chosen based on significant differences in the one-way analysis of variance or chi-square tests. Independent variables were entered simultaneously in the logistic regressions. In study V, predictors of adherence and remission were estimated with logistic regressions.

Independent sample t-tests were used to compare means in study I and to evaluate compliance with LT and potential effect of season in study III. Spearman’s rank correlation coefficient (Spearman’s ρ) was used in study II to quantify the relation between DLMO, MEQ score, and sleep-wake pattern. Spearman’s ρ was also used to quantify the relation between each measure of LT compliance and the change in each outcome variable from baseline to week 2. Furthermore, Spearman’s ρ was used to evaluate if the perceived credibility and expectations of CBT (CEQ score) were associated with compliance and treatment effect (number of CBT sessions attended and change in each outcome variable from week 2 to week 6).

Paired-sample t-tests were used to investigate the change in sleep onset, sleep offset, and daytime functioning from baseline to end of treatment in
study V. Analyses performed to examine the effects of CBT on sleep onset, sleep offset, sleep duration, sleep quality, ISI score, ESS score, HADS-A score, and HADS-D score were based on a group (LT-NT, LT+CBT) × time (2 week, 6 week, 6 month) randomized design with the intent-to-treat model. Linear mixed models (Brown, 1999) were employed to avoid imputation of missing data. The mixed model tested group, time, and interaction effects for continuous dependent variables. Estimated parameters were obtained using a mixed-models approach employing a first order autoregressive covariance structure. A priori contrasts were employed to investigate specific hypotheses, e.g., differences before and after treatment and maintenance of treatment gains at follow-up.

Within-group effect sizes (Cohen’s $d$) were calculated (Cohen, 1988) in studies III and V. Between-group effect sizes (Cohen’s $d$) were calculated in study III. Cohen (1988) proposed a 3-fold classification of within-group and between-group effect sizes: small (0.20–0.49), medium (0.50–0.79), and large ($\geq0.80$).

Regression analyses were used to assess the predictive value of patient characteristics at baseline for the defined outcome measures. Each candidate predictor was examined in a separate multiple linear regression model, using the baseline value of the outcome variable of interest as a covariate. For each outcome, variables associated with the outcome with $p < 0.05$ were then simultaneously included in a multiple linear regression model.
Results

Prevalence of DSPD and correlations with sleep related questions

Among the study participants, 8.6% (n = 58) fulfilled criterion A. Among those who fulfilled criterion A, 77.2% (n = 44) fulfilled criterion B, 63.8% (n = 37) fulfilled criterion C, and 64% (n = 38) had had a DSP for 3 months or more. The prevalence of DSP was 4.6% (n = 31) and that of DSPD was 4.0% (n = 27) in the total sample (n = 671).

Persons with DSP and DSPD exhibited significantly more difficulty in waking up before 09:00 am than persons without DSP. These individuals also demonstrated significantly lower scores on the rMEQ (indicating an eveningness chronotype) than persons without DSP. The proportion of participants with late arrivals in the morning (more than once per week) and sleep duration of <7 h was higher in the DSPD group than in the group with no delayed sleep phase. Persons with DSPD also had significantly higher ISI scores and significantly more difficulty changing sleep onset time than persons without DSP and persons with only a DSP, see Table 4.
Table 4. Responses to DSPD-related questions used to assess the validity of the DSM-V diagnostic criteria for the sleep disorder

<table>
<thead>
<tr>
<th></th>
<th>No delayed sleep phase (n = 613)</th>
<th>DSP (n = 31)</th>
<th>DSPD (n = 27)</th>
<th>No delayed sleep phase vs. DSP</th>
<th>No delayed sleep phase vs. DSPD</th>
<th>DSP vs. DSPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep duration &lt; 7 h</td>
<td>34.4</td>
<td>35.5</td>
<td>55.6</td>
<td>n.s.</td>
<td>$\chi^2 = 4.49, p &lt; 0.05$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Late arrival at work or school</td>
<td>13.8</td>
<td>19.4</td>
<td>33.3</td>
<td>n.s.</td>
<td>$\chi^2 = 7.40, p &lt; 0.05$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Difficulty falling asleep earlier</td>
<td>2.24 ± 1.00</td>
<td>2.55 ± 1.15</td>
<td>3.44 ± 1.12</td>
<td>n.s.</td>
<td>$t = -6.06, p &lt; 0.001$</td>
<td>$t = -3.00, p &lt; 0.05$</td>
</tr>
<tr>
<td>Difficulty waking up at 09:00 h</td>
<td>1.45 ± 0.72</td>
<td>2.06 ± 1.18</td>
<td>2.52 ± 1.01</td>
<td>$t = -2.85, p &lt; 0.01$</td>
<td>$t = -5.40, p &lt; 0.001$</td>
<td>n.s.</td>
</tr>
<tr>
<td>ISI score</td>
<td>8.27 ± 5.60</td>
<td>7.57 ± 4.31</td>
<td>16.30 ± 3.89</td>
<td>n.s.</td>
<td>$t = -10.25, p &lt; 0.001$</td>
<td>$t = -8.00, p &lt; 0.01$</td>
</tr>
<tr>
<td>rMEQ score</td>
<td>13.59 ± 3.34</td>
<td>8.55 ± 2.71</td>
<td>8.48 ± 2.01</td>
<td>$t = 8.25, p &lt; 0.001$</td>
<td>$t = 12.47, p &lt; 0.001$</td>
<td>n.s.</td>
</tr>
<tr>
<td>ESS score</td>
<td>7.80 ± 4.02</td>
<td>7.10 ± 4.47</td>
<td>8.85 ± 4.44</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are mean ± SD score or percentage of participants in the No delayed sleep phase, DSP and DSPD group respectively. DSP, delayed sleep phase; DSPD, delayed sleep phase disorder; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; n.s., non significant; rMEQ, reduced Horne Östberg Morningness-Eveningness Questionnaire; SD, standard deviation. Exclusion of questions 1, 5, and 7 from the ISI and question 1 from the rMEQ did not change the pattern of results.
Table 5. Demographic and clinical characteristics of persons with no delayed sleep phase, DSP, and DSPD

<table>
<thead>
<tr>
<th></th>
<th>No delayed sleep phase (n = 610)</th>
<th>DSP (n = 31)</th>
<th>DSPD (n = 27)</th>
<th>No delayed sleep phase vs. DSP</th>
<th>No delayed sleep phase vs. DSPD</th>
<th>DSP vs. DSPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>21.79 ± 3.14</td>
<td>21.77 ± 2.85</td>
<td>21.19 ± 2.90</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57.2</td>
<td>29.0</td>
<td>44.4</td>
<td>χ² = 9.50, p &lt; 0.05</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>No occupation</td>
<td>3.8</td>
<td>16.1</td>
<td>29.6</td>
<td>χ² = 10.08, p &lt; 0.05</td>
<td>χ² = 35.56, p &lt; 0.001</td>
<td>n.s.</td>
</tr>
<tr>
<td>Living alone</td>
<td>25.8</td>
<td>29.0</td>
<td>40.7</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychiatric condition</td>
<td>8.2</td>
<td>0</td>
<td>18.5</td>
<td>n.s.</td>
<td>n.s.</td>
<td>χ² = 6.28, p &lt; 0.05</td>
</tr>
<tr>
<td>Medical condition</td>
<td>9.5</td>
<td>9.7</td>
<td>7.4</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Shift work</td>
<td>8.6</td>
<td>25</td>
<td>15.4</td>
<td>χ² = 8.49, p &lt; 0.05</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>18.1</td>
<td>51.7</td>
<td>33.3</td>
<td>χ² = 18.87, p &lt; 0.001</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>11.3</td>
<td>35.5</td>
<td>18.5</td>
<td>χ² = 17.45, p &lt; 0.001</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Drug use</td>
<td>3.9</td>
<td>16.1</td>
<td>11.1</td>
<td>χ² = 9.57, p &lt; 0.05</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Three-item PSWQ score</td>
<td>6.91 ± 3.17</td>
<td>5.84 ± 3.08</td>
<td>8.31 ± 3.04</td>
<td>n.s.</td>
<td>t = -2.20, p &lt; 0.05</td>
<td>t = -2.20, p &lt; 0.01</td>
</tr>
<tr>
<td>SRS score</td>
<td>20.63 ± 6.70</td>
<td>17.23 ± 5.67</td>
<td>22.92 ± 7.05</td>
<td>t = 2.72, p &lt; 0.01</td>
<td>n.s.</td>
<td>t = -3.35, p &lt; 0.01</td>
</tr>
<tr>
<td>HADS-anxiety score ≥ 8</td>
<td>36.0</td>
<td>25.8</td>
<td>66.7</td>
<td>χ² = 10.40, p &lt; 0.01</td>
<td>χ² = 9.74, p &lt; 0.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>HADS-depression score ≥ 8</td>
<td>7.4</td>
<td>6.5</td>
<td>22.2</td>
<td>n.s.</td>
<td>χ² = 7.71, p &lt; 0.05</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percent. DSP, delayed sleep phase; DSPD, delayed sleep phase disorder; HADS, Hospital Anxiety and Depression Scale; PSWQ, Penn State Worry Questionnaire; SD, standard deviation; SRS, Symptom-Focused Rumination Scale.
Table 6. Results of multiple logistic regression analysis of factors associated with DSP relative to no delayed sleep phase (Table 6a), DSPD relative to no delayed sleep phase (Table 6b), and DSP relative to DSPD (Table 6c)

<table>
<thead>
<tr>
<th>6a</th>
<th>Significance</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>n.s.</td>
<td>1.87</td>
<td>0.72–4.90</td>
</tr>
<tr>
<td>No occupation</td>
<td>p &lt; 0.001</td>
<td>11.10</td>
<td>3.22–38.27</td>
</tr>
<tr>
<td>Shift work</td>
<td>p &lt; 0.01</td>
<td>4.67</td>
<td>1.63–13.36</td>
</tr>
<tr>
<td>Drug use</td>
<td>n.s.</td>
<td>3.68</td>
<td>0.98–13.82</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>p &lt; 0.05</td>
<td>3.04</td>
<td>1.09–8.50</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>p &lt; 0.05</td>
<td>3.44</td>
<td>1.40–8.46</td>
</tr>
<tr>
<td>SRS score</td>
<td>p &lt; 0.05</td>
<td>1.08</td>
<td>1.00–1.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6b</th>
<th>Significance</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No occupation</td>
<td>p &lt; 0.001</td>
<td>10.04</td>
<td>3.76–26.83</td>
</tr>
<tr>
<td>Three-item PSWQ score</td>
<td>n.s.</td>
<td>1.02</td>
<td>0.87–1.19</td>
</tr>
<tr>
<td>HADS-anxiety score ≥ 8</td>
<td>p &lt; 0.05</td>
<td>3.17</td>
<td>1.32–7.61</td>
</tr>
<tr>
<td>HADS-depression score ≥ 8</td>
<td>n.s.</td>
<td>1.77</td>
<td>0.60–5.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6c</th>
<th>Significance</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS score</td>
<td>n.s.</td>
<td>1.10</td>
<td>0.97–1.24</td>
</tr>
<tr>
<td>Three-item PSWQ score</td>
<td>n.s.</td>
<td>1.02</td>
<td>0.77–1.35</td>
</tr>
<tr>
<td>HADS-anxiety score &lt; 8</td>
<td>n.s.</td>
<td>0.39</td>
<td>0.09–1.77</td>
</tr>
</tbody>
</table>

CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; n.s., non-significant; OR, odds ratio; PSWQ, Penn State Worry Questionnaire; SRS, Symptom-Focused Rumination Scale.

Factors associated with DSP versus no delayed sleep phase

The socio-demographic and clinical characteristics of the no delayed sleep phase and DSP groups are shown in Table 5. The proportion of shift workers
was significantly higher in the DSP group than in the no delayed sleep phase group, and there were also significantly more men than women in this group. The SRS score was lower in the DSP group, and the prevalence of nicotine use, frequent consumption of alcohol, and any use of drugs were higher in the DSP group than in the no delayed sleep phase group. The proportion of persons unemployed or on sick leave was higher in the DSP group than in the no delayed sleep phase group.

Logistic regression analysis revealed that being unemployed or on sick leave, working shift work, using nicotine, consuming alcohol at least twice per week, and lower rumination were significantly associated with DSP. See Table 6a for odds ratios.

Factors associated with DSPD versus no delayed sleep phase
The proportion of persons unemployed or on sick leave was higher in the DSPD group than in the no delayed sleep phase group. Scores on the three-item PSWQ were higher in the DSPD group than in the no delayed sleep phase group, and the proportion of persons with anxiety and depression ≥8 points on HADS-anxiety and -depression subscales, respectively) was higher in the DSPD group than in the no delayed sleep phase group (Table 5).

Logistic analyses revealed that being unemployed or on sick leave and having anxiety were significantly associated with DSPD. See Table 6b for odds ratios.

Factors associated with DSP versus DSPD
The proportion of persons who reported a psychiatric condition was higher in the DSPD group than in the DSP group. Worry (three-item PSWQ score) and rumination (SRS score) were significantly higher in the DSPD group than in the DSP group, and the proportion of persons with anxiety ≥ 8 points on HADS-anxiety subscale) was also higher (Table 5).

Logistic regression analysis did not reveal any factors significantly associated with DSPD. See Table 6c for odds ratios. The proportion of persons with a psychiatric condition could not be entered in the logistic regression as the value was zero in the DSP group.
DLMO

DLMO in healthy adults

In study II, mean DLMO was 20:58 h ± 55 min. Mean time of sleep onset was 22:55 h ± 1 h 07 min, and mean time of sleep offset was 06:35 h ± 44 min. The phase angles are presented in Table 7. There were no significant correlations between DLMO and sleep onset or sleep offset. There was a significant difference between sleep offset on weekend days and weekdays (Table 7). There was a tendency toward a correlation between DLMO and sleep onset and sleep offset on nights before workdays (ρ = 0.42; p = 0.13 and ρ = 0.40; p = 0.16, respectively). This tendency was not seen on nights before days off (Friday and Saturday nights; ρ = -0.01; p = 0.96 and ρ = 0.05; p = 0.86, respectively).

The mean MEQ score was 58.8 ± 10.5. Two participants were classified as morning chronotype, eight as normal chronotype, and four as evening chronotype. There was no significant correlation between DLMO and diurnality (ρ = -0.04; n.s.).

DLMO in adolescents and young adults with DSPD

DLMO was obtained in 34 of the 57 young adults with DSPD who participated in the treatment study (studies III, IV, and V). Mean DLMO was 23:24 h ± 1 h 03 min (n = 34). Mean time of sleep onset was 02:50 h ± 1 h 17 min, and mean time of sleep offset was 10:10 h ± 1 h 56 min. There was a significant correlation between DLMO and sleep onset (ρ = 0.70; p < 0.001) and between DLMO and sleep offset (ρ = 0.65; p < 0.001). Time from DLMO to sleep onset was 3 h 28 min ± 58 min (range, 2 h 11 min to 7 h 02 min), and time from DLMO to sleep offset was 10 h 53 min ± 1 h 23 min (range, 8 h 22 min to 15 h 46 min).

Table 7. Difference between DLMO and sleep onset and offset during the whole week, on nights before days off, and on nights before workdays (study II)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DLMO to sleep onset (h:min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The whole week</td>
<td>1:58</td>
<td>1:14</td>
<td>2:17</td>
<td>-00:22</td>
<td>4:05</td>
<td>4:27</td>
</tr>
<tr>
<td>Nights before days off</td>
<td>2:17</td>
<td>1:40</td>
<td>2:08</td>
<td>00:04</td>
<td>6:24</td>
<td>6:20</td>
</tr>
<tr>
<td>Nights before workdays</td>
<td>1:50</td>
<td>1:10</td>
<td>2:05</td>
<td>-00:32</td>
<td>3:14</td>
<td>3:46</td>
</tr>
<tr>
<td>Difference between</td>
<td>0:27</td>
<td>1:08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nights before days off</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and workdays</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DLMO to sleep offset (h:min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The whole week</td>
<td>9:38</td>
<td>1:02</td>
<td>9:32</td>
<td>7:47</td>
<td>12:04</td>
<td>4:17</td>
</tr>
</tbody>
</table>

42
Results from the treatment study (Paper III, IV and V)

LT compliance

During the 2 weeks of LT, 18 of the 44 participants (42%) used the lamp every day during treatment, 14 participants (33%) used the LT lamp on 12 or 13 days, seven participants (16%) used the LT lamp on 10 or 11 days, and four participants (9%) used the lamp on fewer than 10 days. No participants used the lamp on fewer than 6 days. Reported reasons for missing LT sessions were lack of time and forgetfulness. Mean ± SD duration of LT was 36 ± 7 min, and participants reported turning on the LT within 13 ± 31 min of sleep offset. During the second week of LT, the mean ± SD difference in the recommended and actual start times of LT was 22 ± 68 min. There were no significant differences between the two treatment groups (LT+CBT, LT+NT) in the number of days of LT use ($p = 0.95$), duration of LT ($p = 0.31$), difference in the recommended and actual start time ($p = 0.78$), or time from sleep offset to LT treatment ($p = 0.48$). There were no significant correlations between the number of days of LT use or the duration of LT and the change in any outcome measure from baseline to the week 2 assessment. There was a significant correlation between the difference in recommended and actual start times of LT and the change in sleep offset from baseline to the week 2 assessment ($r = -0.42; p = 0.01$), whereby a smaller difference in the recommended and actual start times was associated with an greater advance in sleep offset from baseline to the week 2 assessment. There was no significant difference in any outcome measure at the week 2 assessment between participants who started LT in September, October, or November and participants who started LT in January, February, or March.

CBT compliance and credibility/expectancy

Eight participants in the LT+CBT group attended all four CBT sessions, five participants attended three CBT sessions, and four participants attended two CBT sessions. Reasons for missing CBT sessions were lack of time because of school or work. There were no significant correlations between number of CBT sessions attended and the change in any outcome measure from the week 2 to the week 6 assessment.
In the QEQ questionnaire participants rated CBT as logical ($M = 7.4$, $SD = 0.9$) and with utility ($M = 6.2$, $SD = 1.0$), had confidence in recommending the treatment ($M = 6.5$, $SD = 1.1$), and felt that it would be of help ($M = 5.8$, $SD = 1.3$). The logical rating score was similar to that reported for cognitive therapy or CBT for insomnia ($M = 7.8–7.9$) (Harvey, Sharpney, Ree, Stinson, & Clark, 2007; Jansson-Fröjmark, Harvey, Norell-Clarke, & Linton, 2012), but the utility, confidence, and help ratings were lower than those reported for cognitive therapy or CBT for insomnia. On a scale of 0 to 100, participants rated the extent to which they thought that improvement would occur ($M = 50.0$, $SD = 16.2$) and to which they felt that improvement would occur ($M = 43.5$, $SD = 20.1$). These ratings were both lower than those reported for cognitive therapy and CBT for insomnia ($M = 63–74$ and $61–77$, respectively) (Harvey et al., 2007; Jansson-Fröjmark et al., 2012). There was a significant correlation between the score on the fifth question in the CEQ (extent to which they thought that improvement would occur) and the change in sleep duration from the week 2 to week 6 assessment ($r = 0.60$, $p = 0.03$), whereby a higher score on the CEQ question correlated with greater increase of the sleep duration. There were no other significant correlations between the CEQ question scores and change in outcome measures from week 2 to week 6.

The effect of LT with scheduled rise times

Sleep onset significantly advanced from baseline to the end of treatment ($t = 5.58$, $p < 0.001$). Sleep offset also significantly advanced from baseline to the end of treatment ($t = 7.72$, $p < 0.001$; Table 8, Figure 2a, and b).

Adherence to the LT schedule (sleep offset before 09:00 h) was observed in 81% ($\chi^2 = 3.08$, $p < 0.001$) of the participants at the end of treatment. At baseline, 23% of the participants already woke up earlier than 09:00 h. Remission (sleep onset before 01:00 h and sleep offset before 09:00 h) was observed in 45% ($\chi^2 = 42.02$, $p < 0.001$) of the participants at the end of treatment. There was a significant improvement in daytime functioning from baseline to the end of treatment ($t = 4.50$, $p < 0.001$) and a significant improvement in insomnia symptoms (ISI score). Symptoms of depression, anxiety, and daytime sleepiness were not significantly altered after the 2 weeks of LT.
Figure 2 Mean sleep onset (a) and sleep offset (b) at baseline and during light therapy. Error bars are calculated as standard error of the mean.
Table 8. Outcome measures at baseline and after 2 weeks of LT

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Baseline</th>
<th>Week 2 assessment</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset</td>
<td>03:00 h ± 1 h 20 min</td>
<td>01:27 h ± 1 h 41 min*</td>
<td>1.33</td>
</tr>
<tr>
<td>Sleep offset</td>
<td>10:22 h ± 2 h 02 min</td>
<td>8:05 h ± 1 h 29 min*</td>
<td>1.29</td>
</tr>
<tr>
<td>Daytime functioning</td>
<td>5.20 ± 1.5</td>
<td>4.02 ± 1.91*</td>
<td>0.71</td>
</tr>
<tr>
<td>Sleep duration, h</td>
<td>7.03 ± 1.26</td>
<td>6.84 ± 1.01</td>
<td>0.17</td>
</tr>
<tr>
<td>Sleep quality (range 1–5)</td>
<td>3.16 ± 1.23</td>
<td>2.29 ± 0.54*</td>
<td>0.98</td>
</tr>
<tr>
<td>ISI score (range 0–28)</td>
<td>15.55 ± 4.08</td>
<td>11.29 ± 5.00*</td>
<td>0.94</td>
</tr>
<tr>
<td>ESS score (range 0–24)</td>
<td>6.86 ± 3.77</td>
<td>6.08 ± 3.83</td>
<td>0.18</td>
</tr>
<tr>
<td>HADS-A score (range 0–21)</td>
<td>7.39 ± 4.67</td>
<td>7.16 ± 3.97</td>
<td>-0.04</td>
</tr>
<tr>
<td>HADS-D score (range 0–21)</td>
<td>4.93 ± 2.93</td>
<td>5.07 ± 3.82</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± SD. ESS, Epworth Sleepiness Scale; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, depression subscale of the Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index.
* p < 0.001.

Predictors of the effect of LT with scheduled rise times

After controlling for baseline sleep onset (p < 0.05), linear regression analysis revealed that the number of LT days (p < 0.05) predicted advance in sleep onset at the end of treatment (Table 2).

After controlling for baseline sleep offset (p < 0.01), the number of LT days (p < 0.05) and DLMO (p < 0.05) predicted advance in sleep offset at the end of treatment (Table 2). DLMO was only available for 25 of the 44 study participants. A multiple linear regression analysis conducted using this subgroup of 25 participants indicated that the number of LT days (p < 0.05) and DLMO (p < 0.05) remained as predictors of sleep offset at the end of treatment. Baseline sleep offset was no longer significant in the multiple linear regression analysis.

There were no significant predictors of adherence to the scheduled LT (sleep offset at 09:00 h or earlier). Logistic regressions performed after excluding participants with a baseline sleep offset of 09:00 h or earlier demonstrated comparable odds ratios to those performed before excluding these
participants. There were no significant predictors of remission (sleep onset before 01:00 h and sleep offset before 09:00 h; Table 3).

After controlling for daytime functioning at baseline ($p < 0.001$), a lower level of depressive symptoms ($p < 0.05$) and a less pronounced eveningness chronotype ($p < 0.05$) at baseline both predicted better daytime functioning after 2 weeks of LT (Table 2). In a multiple linear analysis, only a less pronounced eveningness chronotype ($p < 0.05$) and lower baseline daytime functioning ($p < 0.05$) remained as predictors of poor daytime functioning after 2 weeks of LT.

**Effect of CBT**

Before CBT was started there were no interaction effect between groups (LT+CBT and LT+NT) for sleep onset ($F=0.01$, $p=0.95$), sleep offset ($F=0.09$, $p=0.76$), sleep duration ($F=0.22$, $p=0.88$), sleep quality ($F=0.94$, $p=0.34$), ESS ($F=2.97$, $p=0.10$), HADS-A ($F=0.01$, $p=0.96$) after LT, or HADS-D ($F=2.91$, $p=0.10$), but the LT+CBT group had a significantly larger improvement in severity of sleep difficulties than the LT+NT group ($F=5.92$, $p=0.02$).

The descriptive statistics, within-group effect sizes, and between-group effect sizes are displayed in Table 9. Mixed model analysis was used for the sleep diary and questionnaire data.

There was no significant effect of group ($F = 0.17$, $p = 0.68$) or time ($F = 2.09$, $p = 0.133$) on sleep onset, and no significant interaction ($F = 1.13$, $p = 0.33$). There was no significant effect of group ($F = 1.67$, $p = 0.20$) on sleep offset, but there was a significant effect of time ($F = 9.54$, $p < 0.001$), indicating a delay in sleep offset in the whole sample. There was no significant interaction between group and time for sleep offset ($F = 0.42$, $p = 0.66$).

There was no significant effect of group ($F < 0.001$, $p = 1.00$) on sleep duration, but there was a significant effect of time ($F = 20.23$, $p < 0.001$), indicating an increase in sleep duration over time in the whole sample. There was also a significant interaction between group and time ($F = 4.33$, $p = 0.02$). Additional analyses showed that the increase in sleep duration from week 2 to week 6 was greater in the CBT group than in the NT group ($p = 0.04$) and the decrease in sleep duration from week 2 to the 6 month follow-up was also greater in the CBT group than in the NT group ($p = 0.01$).

There was no significant effect of group ($F = 0.04$, $p = 0.85$) on sleep quality, but there was a significant effect of time ($F = 40.25$, $p < 0.001$), indicating improvement in sleep quality over time in the whole sample. There was no significant interaction between group and time ($F = 0.72$, $p = 0.49$).

There was a significant effect of group ($F = 5.05$, $p = 0.03$) and time ($F = 7.39$, $p < 0.001$) on the severity of sleep difficulties. Post hoc tests indicated significantly lower scores already at week 2 for the CBT group, and an improvement in the severity of sleep difficulties over time in both groups.
There was no interaction between group and time for severity of sleep difficulties ($F = 0.44, p = 0.65$).

There was no significant effect of group ($F = 0.02, p = 0.97$) on daytime sleepiness, but there was a significant effect of time ($F = 10.01, p < 0.001$). Daytime sleepiness increased from week 2 to week 6 and then decreased from week 6 to the 6 month follow-up (Table 4). There was no significant interaction between group and time for daytime sleepiness ($F = 2.92, p = 0.06$).

There was no significant effect of group ($F = 0.08, p = 0.79$) or time ($F = 0.69, p = 0.51$) on anxiety, but there was a significant interaction between group and time ($F = 3.44, p = 0.04$). Additional analyses showed that the decrease in anxiety from week 2 to week 6 was greater in the CBT group than in the NT group ($p = 0.02$), and the decrease from week 6 to the 6 month follow-up was also greater ($p = 0.04$).

There was no significant effect of group ($F = 0.07, p = 0.80$) or time ($F = 0.42, p = 0.66$) on depression, but there was a significant interaction between group and time ($F = 4.00, p = 0.02$). Additional analyses showed that the decrease in depression from week 2 to the 6 month follow-up was greater in the CBT group than in the NT group ($p = 0.01$), and the decrease from week 6 to the 6 month follow-up was also greater ($p = 0.01$).
Table 9. Sleep variables at the week 2 and week 6 assessments (start and end, respectively, of the CBT), and at the 6 month follow-up assessment

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 2 assessment [M ± SD]</th>
<th>Week 6 assessment [M ± SD]</th>
<th>Within-group <em>d</em></th>
<th>Between-group <em>d</em></th>
<th>6 month assessment [M (SD)]</th>
<th>Within-group <em>d</em></th>
<th>Between-group <em>d</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset</td>
<td>LT+CBT</td>
<td>01:19 h ± 1 h 24 min</td>
<td>01:26 h ± 1 h 29 min</td>
<td>0.08</td>
<td>01:22 h ± 1 h 31 min</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LT+NT</td>
<td>01:07 h ± 1 h 26 min</td>
<td>01:53 h ± 1 h 32 min</td>
<td>0.53</td>
<td>01:38 h ± 1 h 32 min</td>
<td>0.36</td>
<td>0.18</td>
</tr>
<tr>
<td>Sleep offset</td>
<td>LT+CBT</td>
<td>08:09 h ± 1 h 24 min</td>
<td>09:11 h ± 1 h 32 min</td>
<td>0.71</td>
<td>08:55 h ± 1 h 31 min</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LT+NT</td>
<td>08:18 h ± 1 h 26 min</td>
<td>09:40 h ± 1 h 34 min</td>
<td>0.92</td>
<td>09:40 h ± 1 h 34 min</td>
<td>0.90</td>
<td>0.48</td>
</tr>
<tr>
<td>Sleep duration, h</td>
<td>LT+CBT</td>
<td>6.75 ± 0.82</td>
<td>7.92 ± 0.87</td>
<td>1.38</td>
<td>7.60 ± 0.87</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LT+NT</td>
<td>7.03 ± 0.83</td>
<td>7.50 ± 0.92</td>
<td>0.54</td>
<td>7.74 ± 0.87</td>
<td>0.84</td>
<td>0.16</td>
</tr>
<tr>
<td>Sleep quality (range 1–5)</td>
<td>LT+CBT</td>
<td>2.4 ± 0.8</td>
<td>3.7 ± 1.0</td>
<td>1.44</td>
<td>4.0 ± 0.9</td>
<td>1.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LT+NT</td>
<td>2.4 ± 0.8</td>
<td>3.9 ± 0.9</td>
<td>1.88</td>
<td>3.7 ± 0.9</td>
<td>1.65</td>
<td>0.33</td>
</tr>
</tbody>
</table>

CBT, cognitive behavioral therapy; *d*, Cohen’s d; LT, light therapy; M, mean; NT, no treatment; SD, standard deviation.

*a*From week 2 to week 6 assessment. *b*From week 2 to the 6 month follow-up assessment.
Table 10. Symptoms related to DSPD at the week 2 and week 6 assessments (start and end, respectively, of the CBT), and at the 6 month follow-up assessment

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 2 assessment [M ± SD]</th>
<th>Week 6 assessment [M ± SD]</th>
<th>Within-group d&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Between-group d&lt;sup&gt;a&lt;/sup&gt;</th>
<th>6-month assessment [M ± SD]</th>
<th>Within-group d&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Between-group d&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT+CBT</td>
<td>9.9 ± 4.4</td>
<td>8.4 ± 4.5</td>
<td>-0.34</td>
<td></td>
<td>6.2 ± 4.5</td>
<td>-0.83</td>
<td></td>
</tr>
<tr>
<td>LT+NT</td>
<td>12.2 ± 4.4</td>
<td>11.1 ± 4.4</td>
<td>-0.25</td>
<td>0.61</td>
<td>9.9 ± 4.8</td>
<td>-0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>ISI score (range 0–28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT+CBT</td>
<td>7.3 ± 4.2</td>
<td>8.8 ± 4.4</td>
<td>0.30</td>
<td></td>
<td>6.9 ± 4.7</td>
<td>-0.09</td>
<td></td>
</tr>
<tr>
<td>LT+NT</td>
<td>6.5 ± 3.9</td>
<td>11.1 ± 4.2</td>
<td>1.06</td>
<td>0.58</td>
<td>5.3 ± 4.8</td>
<td>-0.26</td>
<td>0.34</td>
</tr>
<tr>
<td>ESS score (range 0–24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT+CBT</td>
<td>5.8 ± 3.9</td>
<td>6.4 ± 3.9</td>
<td>0.15</td>
<td>0.08</td>
<td>6.2 ± 4.0</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>LT+NT</td>
<td>4.2 ± 3.4</td>
<td>4.0 ± 3.5</td>
<td>-0.06</td>
<td>0.23</td>
<td>5.0 ± 3.6</td>
<td>0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>HADS-A score (range 0–21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT+CBT</td>
<td>5.1 ± 3.4</td>
<td>4.8 ± 3.5</td>
<td>-0.09</td>
<td></td>
<td>4.1 ± 3.5</td>
<td>-0.29</td>
<td></td>
</tr>
<tr>
<td>LT+NT</td>
<td>4.2 ± 3.4</td>
<td>4.0 ± 3.5</td>
<td>-0.06</td>
<td>0.23</td>
<td>5.0 ± 3.6</td>
<td>0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>HADS-D score (range 0–21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBT, cognitive behavioral therapy; d, Cohen’s d; ESS, Epworth Sleepiness Scale; HADS-A, anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-D, depression subscale of the Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; LT, light therapy; M, mean; NT, no treatment; SD, standard deviation.

<sup>a</sup>From week 2 to week 6 assessment. <sup>b</sup>From week 2 to the 6 month follow-up assessment.
Clinical outcomes from study III, IV and V

The proportion of participants with sleep onset before 01:00 h was similar in the LT+CBT group and the LT+NT group at the week 2 assessment ($\chi^2 = 0.38, p = 0.85$), week 6 assessment ($\chi^2 = 0.28, p = 0.60$), and 6 month follow-up assessment ($\chi^2 = 2.23, p = 0.14$; Figure 3a).

The proportion of participants with sleep offset before 09:00 h was similar in the LTC+CBT group and the LT+NT group at the week 2 assessment ($\chi^2 = 0.07, p = 0.80$), week 6 assessment ($\chi^2 = 0.32, p = 0.57$), and 6-month follow-up assessment ($\chi^2 = 0.85, p = 0.36$; Figure 3b).

The proportion of participants with an ISI score < 8 was similar in the LT+CBT group and the LT+NT group at the week 2 assessment ($\chi^2 = 1.82, p = 0.18$), week 6 assessment ($\chi^2 = 3.23, p = 0.07$), and 6 month follow-up assessment ($\chi^2 = 0.82, p = 0.37$; Figure 2c). However, the $p$ values suggest a trend for fewer sleep difficulties in the LT+CBT group at the week 6 assessment.
Discussion

DSPD was common among young adults and adolescents with a prevalence of 4% and it was associated with social and mental health problems. Self-administered LT at home with scheduled rise times was effective in advancing sleep-wake rhythm and improving sleep difficulties in DSPD. To add CBT in the treatment of DSPD was well accepted and appreciated by the participants. The compliance to the treatment both the LT and the CBT was quite satisfactory considering that the participants were not compensated.

Prevalence

In the current study, the prevalence of DSPD was 4% and the prevalence of only DSP was 4.6% among Swedish adolescents and young adults. Considering the age span of the study participants, 16–26 years, and the distinction made between DSPD and DSP, the estimated prevalence of DSP and DSPD coincides well with that reported in other recent studies (Paine et al., 2014; Saxvig et al., 2012; Sivertsen et al., 2013).

Diagnostic Aspects

All participants with DSPD have a DSP since a delayed sleep-wake phase is one of the main criteria for the diagnosis. In study I we wanted to separate those with DSPD and those with only a DSP not fulfilling the criteria for DSPD to better understand these two groups.

To validate the three distinct groups, in study I we employed questions that were not part of the criteria for DSPD and DSP. Table 5 demonstrates the responses to the DSPD-related questions utilized to assess the validity of the DSM-V diagnostic criteria for the sleep disorder. The DSPD group reported significant difficulty altering sleep-wake patterns, frequent late arrivals to school or work in the morning, and ISI scores comparable with those seen for severe insomnia (Morin et al, 2011) and in previous research on DSPD (Danielsson et al, 2015). These results do, to some extent, agree with the clinical picture of DSPD, and in this manner confirm the DSM-V diagnostic criteria for DSPD. DSP and DSPD groups presented an equally pronounced eveningness chronotype, according to the rMEQ score. This
indicates that solely a chronotype questionnaire is not sufficient to separate DSP from DSPD.

The use of a physiological marker such as DLMO is recommended as a diagnostic instrument to confirm the delay in circadian rhythm in DSPD. However, melatonin can be measured and the time of DLMO can be calculated in different ways, which results in variability and causes difficulties identifying a diagnostic time limit for DLMO. Another problem is that circadian rhythm changes with age, which suggests that there, should probably be different diagnostic recommendations for different age groups.

Correlations between DLMO and sleep onset and offset have been reported in adolescents (Burgess & Eastman, 2005; Crowley et al, 2006; Martin & Eastman, 2002). This correlation between sleep-wake patterns and DLMO was also observed among the young adults and adolescents in our treatment study. In the randomized controlled trial, we planned to use DLMO to identify the optimal time for awakening and use of the LT lamp. The intention was not to use DLMO to diagnose participants. Even though we did not find any significant differences between participants who had their LT scheduled according to their DLMO and those who had their LT scheduled according to their sleep diary, the design of the study makes it impossible to draw any conclusions about the role of DLMO in administering LT.

Study II was designed to investigate DLMO in healthy adults. We found that DLMO in healthy working adults was in the expected range shown in earlier studies (Pandi-Perumal et al., 2007), thus validating the analytical procedure used, but that DLMO was not significantly associated with sleep timing or diurnal preference. There was large inter-individual variability in the time delay between DLMO and self-recorded sleep onset and sleep offset (Table 1). These results are in accordance with previous findings (Wright et al., 2005; Sletten et al., 2010). There are several possible explanations for this variability. Changes in light exposure during the daytime could be one explanation for the large variability in time delays (Lewy et al., 1980). Polymorphisms in core clock genes (Katzenberg et al., 1998; Archer et al., 2003; Carpen et al., 2006) could also influence the delay between DLMO (used as a marker of circadian phase) and sleep.

### Associated Factors

In line with previous results (Saxvig et al, 2012), persons with DSP reported more frequent use of nicotine, alcohol, and drugs than persons with no delayed sleep phase. Substance use can promote delayed sleep-wake patterns, as nicotine can cause difficulties initiating sleep (Soldatos et al, 1980). In addition, persons with an extreme eveningness chronotype may be more prone to engage in nightly activities, which often include alcohol or drugs. In contrast to other studies on DSP (Saxvig et al, 2012; Sivertsen et al, 2015), we found that persons with DSP did not have more depressive or
anxiety symptoms than persons with no delayed sleep phase. However, in previous studies, DSP participants included possible DSPD cases. Decreased rumination was associated with DSP, and none of the participants with DSP reported any psychiatric condition. This was somewhat surprising. However, there were persons with DSP reporting elevated levels of anxiety and depression, indicating that there might have been an under-reporting of mental health problems, but this is difficult to interpret. It is also possible that persons with DSP possess factors that make them more resilient to develop psychiatric conditions despite their DSP.

DSP was associated with being without work or educational activity. This has many possible explanations. DSP in combination with substance use or abuse, which seems to be associated with DSP, might cause dropout from school and unemployment. Additionally, there is no pressing need to arise at a certain time in the morning when you do not have an occupation which might cause a further delay of the sleep-wake rhythm. Not surprisingly, shift work was associated with DSP in the current study. Although shift work can lead to delayed sleep patterns, it is also possible that persons with a delayed sleep-wake preference seek work that deviates from a regular nine-to-five schedule.

In agreement with earlier research (Dagan et al., 1998), we found that the prevalence of an elevated level of anxiety or depression was higher among persons with DSPD than persons with no delayed sleep phase. A reason for this might be the shortened sleep duration observed in the DSPD group, as short sleep duration is associated with both anxiety and depression (Pasch et al, 2010; Wolfson & Carskadon, 1998). Furthermore, anxiety is associated with sleep difficulties in general (Gregory & Sadeh, 2012). Alternatively some of the personality traits observed in DSPD are often associated with anxiety and depressive symptoms (Clark et al., Chioquita & Stiles, 2004; Sharma, 2003).

Because of the differences between DSPD and those with only a DSP it seems reasonable to assess DSP and DSPD as distinct entities in future studies.

Treatment Concepts
Effects of LT with scheduled rise times
After the treatment, there was an advance in sleep onset and sleep offset. LT was scheduled in the morning; therefore, sleep offset was also a measure of how well the participants adhered to the scheduled rise time. Persons with DSPD have great difficulties rising early in the morning; however, it is noteworthy that over 80% of the participants had a rise time of 09:00 h or earlier at the end of the 2 weeks of LT. Although a scheduled rise time can advance sleep-wake and circadian rhythm (Saxvig et al, 2014; Sharkey et al,
2011), in the present study it is not possible to differentiate the effect of the scheduled sleep offset from that of LT effect on the observed outcome. The effect of the scheduled rise times can be observed in Figure 2b where a large advancement in sleep offset is demonstrated already on day 1. This advancement on day 1 was probably not solely related to the introduction of LT. It should also be noted that it was a longer time span (3-4 weeks) from baseline to day 1 of LT. However, LT with a scheduled rise time advanced sleep onset, and 45% of the participants went into remission, i.e., fell asleep before 01:00 h and woke up by 09:00 h at the end of treatment.

Daytime dysfunction or distress caused by DSP is one of the criteria for DSPD (Dagan, Stein, et al., 1998; American Academy of Sleep Medicine, 2014). After LT, there was a significant improvement in daytime functioning, indicating that LT not only advanced the sleep-wake rhythm, but also reduced insomnia symptoms and improved daytime functioning. This finding is in accordance with previous research (Gradisar, Dohnt, et al., 2011; Wilhelmsen-Langeland et al., 2013).

Generally about CBT in DSPD

CBT has recently started to be discussed and evaluated as an additive treatment in DSPD (Gradisar, Dohnt, et al., 2011; Lack & Wright, 2007). The administration and efficacy of CBT in DSPD is still not fully explored. For example the amount of therapy sessions, how the therapy should be administered (i.e. in group, individually or in a self-help approach) if it should be administered before, during or after LT or perhaps melatonin treatment is not known today.

In our study most participants appreciated the group format of the CBT, since they met persons with similar sleep problems and in that way felt less stigmatization and worry. The two components that were described as easiest to understand and implement was the relaxation training and cognitive restructuring and the component that was reported as less easy to implement was the sleep regulation.

It is known that the credibility and expectancy of a treatment can affect the outcome (Haanstra et al., 2015; Kim, Roth, & Wollburg, 2015). The participants in our study felt that the treatment model presented at the first CBT session was credible, i.e. linking DSPD symptomatology to maintaining factors as well as providing ideas of how to improve symptomatology. However, the participants expectancy of the treatment with CBT was lower than what is normally observed in persons with Insomnia (Harvey, et al., 2007; Jansson-Fröjmark et al., 2012). This might have been due to lower motivation, a sense of learned helplessness (from previous failures to change their sleep-wake rhythm) or a strict biological view of the disorder.
The effect of adding CBT to LT

The primary endpoints were changes in sleep onset and offset after the LT+CBT or LT+NT, both at week 6 and at 6 month follow-up. There were no statistically significant differences between the groups in sleep onset or sleep offset.

A recent study reported an advance in sleep onset of about 49 min on school days and about 1 h 24 min on weekends 6 months after bright light treatment and CBT (Gradisar, Dohnt, et al., 2011). In the present study, sleep onset advanced approximately 1 h 50 min during the second week of LT, and this was maintained at 6 months. The larger advancement in sleep onset observed in the present study may be due to differences in study populations. Participants in the present study had a later sleep onset and sleep offset at baseline and were older than participants in the previous study (Gradisar, Dohnt et al., 2011).

In the treatment studies sleep difficulties were a major problem for the participants and at baseline ISI-score was similar to that observed in persons with moderate insomnia (Bastien et al, 2001). However, LT+CBT was not superior to LT+NT in maintaining sleep-wake rhythm or improving sleep difficulties. This might be due to the fact that, when entering the study and when LT treatment was started, all participants received some basic information about sleep hygiene, their diagnosis, DLMO, and the importance of a stable sleep-wake rhythm. Another possible reason is that not all persons with DSPD may benefit from CBT. A third possible reason is that the study only included a small number of participants.

Sleep duration and sleep quality were significantly increased in both the LT+CBT and the LT+NT group. At week 6, the increase in sleep duration from week 2 was larger for the LT+CBT group than the LT+NT group.

In the current study, anxiety and depression were measured using the HADS. The HADS-A scores at baseline were similar to those previously reported in persons with DSP (Saxvig, et al., 2012). The HADS-D score was somewhat low in our study. This might be due to the exclusion criteria, whereby persons who were medicating with any antidepressants or had any severe psychiatric illness were excluded. Nevertheless a significantly greater decrease in HADS-A and HADS-D scores were observed in the LT+CBT group as compared to the LT+NT group.

Predictors of the effect of LT with scheduled rise times

The number of LT days was a predictor of earlier sleep onset and earlier sleep offset, underlining the importance of daily usage of LT during treatment. In this study, the duration of LT did not predict the LT effect. In line with these results, a recent study reported that 45 min of LT was not associated with a greater advancement in sleep-wake rhythm than 30 min of LT (Chang et al., 2012). Furthermore, it was recently suggested that 30 min of
morning bright light is effective and feasible for use in the clinic (Crowley & Eastman, 2015). Our results stress the importance of using the LT lamp daily for at least 30 min in the morning.

It is already known that psychoeducation can increase adherence to LT and enhance successful results. In the present study, participants with DSPD received information about their DLMO and why the LT was scheduled daily at a certain time. Addition of CBT could further motivate daily usage of LT and improve the outcome (Gradisar, Dohnt, et al., 2011; Lack & Wright, 2007).

A strong correlation has been reported between sleep-wake rhythm and DLMO in young adults (Burgess et al., 2003; Martin & Eastman, 2002). In the present study, persons with a more severe delay in DLMO had later sleep offset at the end of LT, but DLMO did not predict adherence to the LT schedule.

Limitations

Study I is a cross sectional; therefore, it is only possible to speculate about what might be a risk factor for or a consequence of DSP and DSPD. Longitudinal studies are needed to address the issue of causality. In this cohort DSPD was not diagnosed using sleep diaries. Only one published study has used the gold standard of sleep diaries and actigraphy for diagnosing DSPD (Lovato et al., 2013). This approach to diagnosis might decrease the response rate and be unpractical in epidemiological studies, given the potential difficulty in procuring large numbers of participants from the general population. For this reason, we used a mailed questionnaire to screen for DSPD according to DSM-V criteria. Mental and physical problems were self-reported, and we do not know if they had been diagnosed or in what way they influenced sleep. Future studies might benefit from including a phone screen to better identify mental and physical problems.

Psychiatric disorders are more common in persons with DSPD than in normal sleepers (Dagan et al., 1998; Reid et al., 2012; American Academy of Sleep Medicine, 2014), but we did not enroll persons with psychiatric comorbidities in the treatment study. Future studies may consider including participants with psychiatric disorders to increase the generalizability of results to a broader patient group.

A limitation of studies II and III is the small sample size. In addition, the timing of sleep was self-reported using a sleep diary. Use of an electronic diary or actigraphy may improve the accuracy of this information. On the other hand, it is generally not feasible to use more elaborate physiological measures in real-life studies. Another limitation is that DLMO was not captured for all participants. It would have been interesting to measure DLMO again at the end of the study, but for practical reasons this was not possible.
The exact placement of the lamp, distance of the participant from the lamp, and angle of gaze were not investigated. These factors might influence the response to LT. However, it is difficult to measure these factors in a clinical setting and this would have required a laboratory setting.

Scheduled LT includes both the behavior to rise in the morning and to switch on the LT lamp according to the schedule. In this study, we cannot separate the effect of these two factors. Inclusion of a control group with only a scheduled rise time would have enabled evaluation of this.

Clinical implications

When diagnosing DSPD in the clinic a sleep diary and a thorough sleep anamnesis is mandatory to demonstrate the delayed sleep-wake rhythm and the difficulties and impairment it causes for the individual. Elevated levels of anxiety and depressive symptoms are common in this group. In the treatment studies we did not include persons medicating with antidepressants or persons that had any severe psychiatric illness. This is probably the reason why the depressive and anxiety scores were low at baseline.

One of the strengths of the treatment study is that it was a clinical trial where the participants used a commercially available light box at home. The use of the LT lamp was monitored thorough the scheduled rise time and the sleep diary participants kept throughout the treatment period. The clinical implication of this study is that LT with a scheduled rise time can be conducted at home and that it advances sleep-wake rhythm and improves sleep difficulties on a short and long term basis.

It is feasible to add CBT to LT with scheduled rise times and this treatment regimen seems well accepted in persons with DSPD. The score changes in depressive and anxiety symptoms might possibly provide insight into the participants’ decreased emotional distress. There are still many questions concerning CBT for DSPD that remains unanswered, and future studies should aim to provide answers to these vital notions.
Conclusions

The overall aim of this thesis was to evaluate at-home treatment with Light therapy (LT) and the feasibility of adding cognitive behavior therapy (CBT) to LT in DSPD, furthermore prevalence, diagnostic aspects and associated factors were investigated. DSPD is common among adolescents and young adults and it is associated to negative factors. Both LT alone and LT in combination with CBT gave positive results on the DSPD symptomatology.

Referring to the aims (section 2, page 23) the results may be summarized as:

- DSPD and DSP were common among adolescents and young adults, with a prevalence of 4.0% and 4.6%, respectively, in this Swedish cohort. DSPD was associated with being unemployed and having an elevated level of anxiety. DSP was associated with being unemployed, shift work, substance use, and less rumination.

- The time of DLMO was within the expected time range in healthy working adults and it was not significantly associated with sleep timing or diurnal preference.

- Even though sleep-wake rhythm was not further advanced or better preserved in participants that received LT followed by CBT compared to LT only, the addition of CBT to the DSPD treatment regimen was feasible and well accepted, and had a positive effect on anxiety and depressive symptoms.

- LT with a scheduled rise time can advance sleep-wake rhythm and improve daytime functioning in DSPD. During treatment, the focus should be on consistent, daily use of the LT lamp in the morning, as this was the strongest predictor of an advance in sleep-wake rhythm.


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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)