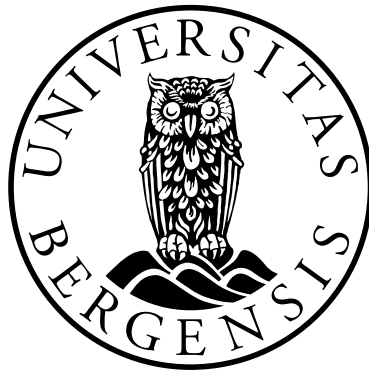# *Delayed Sleep Phase Disorder in Adolescence and Young Adulthood*

Patients` experiences, personality and treatment effects on daytime function

Ane Wilhelmsen-Langeland

Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

2013

"Ehm, okay, my parents and I have fought a lot, because they say `it is your own fault, you don't bother to go to bed at night, and therefore you cannot get up in the morning`."

Participant in the study (quote from paper 1, p. 55)

"(...) I feel that at school everybody perceives me as this slacker (...)"

Participant in the study (quote from paper 1, p. 54)

"(...) it turns out that for me, even if I am pulled out of bed in the morning by my girlfriend, and she also makes sure I go to bed at a reasonable hour over time, I am still just as tired every morning."

*Participant in the study (quote from paper 1, p. 55)*

Contents

Scientific environment

As a PhD-candidate, I have been employed at the Department of Global Public Health and Primary Care, Research group for General Practice, University of Bergen, Norway (2007-2013). I was funded by the Norwegian Research Council (Nevronor) for 3 years and by the Department of Global Public Health and Primary Care for about three quarters of a year. I have for the last part of the work with the thesis been employed part-time by the Norwegian Competence Center for Sleep Disorders (2013), Haukeland University Hospital in Bergen, Norway. A grant (75.000 NOK) was also provided by The Meltzer Foundation which funded parts of the work for the thesis.

The thesis includes results from one large clinical trial conducted in collaboration between The Faculty of Medicine and Dentistry and the Faculty of Psychology. Other results from the same study are presented in the thesis of my colleague Ingvild West Saxvig (thesis title: Delayed Sleep Phase Disorder - Prevalence, sleep, circadian rhythm and treatment). My main supervisor was Professor Bjørn Bjorvatn (Department of Global Public Health and Primary Care, University of Bergen) and co-supervisors were Professor Ståle Pallesen (Department of Psychosocial Science at the Faculty of Psychology, University of Bergen) and Professor Inger-Hilde Nordhus (Department of Clinical Psychology at the Faculty of Psychology, University of Bergen). The first article was a qualitative study with a subsample of the participants in the clinical trial and the main supervisor for this work was associate professor Ingrid Dundas at the Department of Clinical Psychology at the Faculty of Psychology, University of Bergen. Two other researchers were essential in conducting the clinical trial; Ingvild W. Saxvig and Øystein Vedaa. Ingvild W. Saxvig and I recruited participants and collected the data with help from then psychologist student Øystein Vedaa (now a licensed psychologist). Eli Sørensen at the Department of Child and Adolescent Psychiatry, Haukeland University Hospital, Bergen Norway contributed to the second article. Astri Johansen Lundervold at The Department of Biological and Medical Psychology, University of Bergen made important contributions to the third article. Facilities for the trial were the sleep

laboratory at the Faculty of Psychology and were provided by co-supervisor Ståle Pallesen.
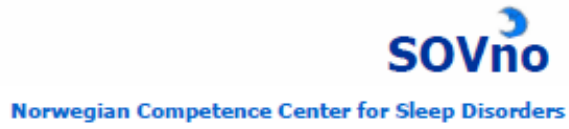
Acknowledgements

The participants in the study deserve the biggest thank you of all. You were amazingly generous in trying to follow all our instructions. I would like to thank my main supervisor **Bjørn Bjorvatn** for being a very present supervisor even though you are extremely busy. You are the impersonation of the saying: "If you need something, ask a busy person". Although frustrating at times to do everything from scratch and by myself (ourselves), I am still glad you made me (us). I would also like to thank you for giving me the opportunity (and confidence) to use my knowledge about sleep and treatment of sleep disorders in a clinical setting. I would like to thank co-supervisor **Ståle Pallesen** who recruited me to this project, I am forever grateful for that. You are easy to ask for help and your answers are always confident and clear. Ståle also deserves thanks for providing the facilities and equipment for the project. I would also like to thank co-supervisor **Inger Hilde Nordhus** for your contribution to the project and clinical expertise. The different skills my three supervisors have provided and the support you have given me is much appreciated.

I would like to thank my colleague **Ingvild West Saxvig** for completing this trial with me. Our tasks have been everything from buying milk, bread and pregnancy tests for the participants to analysing data and writing the articles. There have been more obstacles than any of us could have predicted, but we pulled it off! We completed an RCT while being PhD-candidates (with the help of a total of three maternity leaves) and I know we both are quite proud about that. High five to the both of us! Big thanks also go to **Øystein Vedaa** who helped with recruitment and the data collection. The fact that you stayed through the whole study contributed to making this possible. Also big thanks to **Ingrid Dundas** for supervision on the qualitative study. You contributed enormously to the first article in my thesis and I am grateful for your inspirational patient-centred way of thinking. **Eli Sørensen** made valuable contributions to the second article in my thesis and deserves a thank you. For the third article, **Astri J. Lundervold** helped guiding us in the jungle of neuropsychological tests. Your experience and expertise is wonderful, not to mention your friendliness.

Being part of the sleep research group in Bergen has been a wonderful journey. I appreciate everything I have learned, the people I have met and everything I have experienced in Bergen and at conferences around Europe. Thanks a bunch to the "sleep girls", especially **Siri Waage**, but also **Janne, Jelena, Eldbjørg** and **Elisabeth -** you are much more fun than it sounds!

Thank you to the Research Group for General Practice for inviting me to your board of lecturers as soon as I stepped into my office in the general practice hall in 2007. I have had lectures for students of medicine with a number of you; it has taught me a lot and been a great experience! I thank you also for wanting me as part of your team in the future. I also want to thank you for an inspiring, friendly, philosophical and relaxed environment where PhD-candidates are treated as equally important as professors. You are unique! Especially thanks to the many fellow PhD-candidates over the years for sharing of trivia, personal issues, frustrations and excitement over research and other issues.

I would like to thank my friends who have over many years been curious about my work. A big thank you to my mother **Ingunn Bergland** and father **Ingvard Wilhelmsen,** for bringing me up making me think I could do whatever I wanted in life! I thank you for your support and your love. Many thanks to my father for giving me an outsider's perspective on my thesis. I also thank my sister **Vera Wilhelmsen** for believing in me.

When I started as a PhD-candidate I was single, living downtown Bergen. Since then I met my soul-mate and best friend, **Tore,** bought a great little "countryside" house, got married and had the best (big) little bundles of joy, energy, temper and laughter; **Håkon** (3) and **Ole** (1). You three (plus Molly) are the main reasons the work with this thesis has not completely taken over my life lately, I have refused to miss out on the dinners with you every afternoon and the play time before the boys' bedtime (and my continued workday during the completion of the thesis). I could not ask for a better husband or children, you made my life complete. I love you with all my heart!

List of publications

Paper 1   Wilhelmsen-Langeland, A., Dundas, I., Saxvig, I. W., Pallesen, S., Nordhus, I. H., & Bjorvatn, B. (2012). Psychosocial Challenges Related to Delayed Sleep Phase Disorder. *The Open Sleep Journal, 5,* 51-58.

Paper 2   Wilhelmsen-Langeland, A, Saxvig, I. W., Pallesen, S., Nordhus, I. H., Vedaa, Ø., Sørensen, E., Bjorvatn, B. (2013). The Personality Profile of Young Adults with Delayed Sleep Phase Disorder. *Behavioral Sleep Medicine,* In press.

Paper 3   Wilhelmsen-Langeland, A, Saxvig, I. W., Pallesen, S., Nordhus, I. H., Lundervold, A. J., Vedaa, Ø., Bjorvatn, B. (2013). A randomized controlled trial of treatment for delayed sleep phase disorder. Effects on subjective and objective sleepiness and cognitive function. *Journal of Biological Rhythms,* In press.

Abstract

Delayed sleep phase disorder (DSPD) is a circadian rhythm sleep disorder where the sleep period is delayed compared to conventional norms. Patients with DSPD typically report complaints of excessive daytime sleepiness and impairments in daytime functioning. Patients with DSPD have a rigid circadian rhythm delay which is considered difficult to advance by behavioural means only. The knowledge about this disorder is scarce in the general population as well as in primary health care settings. Limited knowledge often leads for example parents and teachers to view the delayed sleep pattern in the young person as solely due to behaviour or motivational factors. Over time, the young person might also adopt this concept, which adds to the problems innate in the diagnosis. There is also a lack of evidence-based guidelines regarding how to diagnose, examine and treat DSPD.

The first aim of this thesis was to develop a description and exploration of the experiences of patients diagnosed with DSPD regarding their daily challenges and coping mechanisms, by individual in-depth interviews. The second aim was to investigate the personality profile and other psychological aspects of patients with DSPD in a comparative study with healthy controls. The third aim was to assess the effect of treatment with bright light and melatonin on daytime function in patients with DSPD in a randomized controlled trial.

The first paper is a report from a qualitative study with individual in-depth interviews with a sample of 9 participants (16-23 years) diagnosed with DSPD. Analysis was done using systematic text condensation (STC). A core theme in all interviews was how to cope with different challenges related to the disorder. We labelled the identified challenges: 1) To give something up; 2) To blame something or someone; and 3) To have a problem or not. Awareness of these challenges adds to our understanding of the daily struggles of those with DSPD and may improve clinicians` competence and ability to help them.

The study in paper 2 is the first to investigate the NEO-Personality Inventory-Revised (NEO-PI-R) profile of young adults with DSPD. We included 40 patients diagnosed with DSPD (mean age 20.7) and 21 healthy controls (mean age 21.1). Results showed that young adults with DSPD scored higher on Neuroticism, lower on Extroversion and much lower on Conscientiousness than the control group. Assessing the personality profile of young adults with DSPD before initiating treatment might provide a useful clinical guidance regarding the individual needs for follow-up during treatment.

The study in paper 3 was an investigation of short- and long term effects on subjective and objective sleepiness and cognitive function of treatment with bright light and melatonin alongside gradually advanced rise times. The same 40 patients with DSPD from paper 2 participated in the treatment study. Four treatment conditions were used in the short-term intervention (two weeks); dim light (placebo) + placebo capsule, bright light + placebo capsule, dim light (placebo) + melatonin capsule and bright light + melatonin capsule. This was followed by a long-term intervention (three months) including two conditions; no treatment and combined bright light + melatonin. On a gradual advancement of rise time schedule, all treatment conditions (placebo, bright light, melatonin and the combination) were almost equally effective in improving subjective daytime sleepiness, fatigue and cognitive function in the two-week study. Combined bright light and melatonin treatment improved subjective daytime sleepiness, fatigue and cognitive function in the three-month study. Long-term treatment increased some of the positive effects seen after two weeks. The no-treatment group returned to baseline values on most variables in the three-month study.

To conclude, we suggest that caregivers (parents, psychologists, doctors, nurses and others) might be in a better position to help and support young patients with DSPD if they recognize some of the challenges this diagnosis entails. We also suggest that awareness about these challenges should be acknowledged in future research on DSPD. This might increase our understanding of the perceived losses and gains of trying to adapt to a socially accepted sleeping pattern and other challenges faced by youngsters suffering from DSPD, which can influence the emotional consequences of the disorder. Assessing the Big Five personality profile of young adults with DSPD before initiating treatment, might provide a useful clinical guidance regarding the individual needs for follow-up

during treatment. Future studies are warranted to examine the causal relationship of the personality profiles of patients with DSPD. Gradual advancement of rise times seems to be sufficient in producing positive effects on subjective sleepiness, fatigue and cognitive performance in short-term treatment of patients with DSPD. However, the benefits from gradually advanced rise times seemed to wear off, suggesting that continuation of bright light and melatonin treatment is beneficial to maintain positive effects over time.

Sammendrag på norsk

Forsinket søvnfasesyndrom (Delayed sleep phase diosorder; DSPD) er en døgnrytmeforstyrrelse der søvnperioden er forsinket i forhold til konvensjonelle normer. Pasienter med DSPD har plager med overdreven søvnighet på dagtid og redusert fungering på dagtid. Pasienter med DSPD har en rigid døgnrytmeforsinkelse som er vanskelig å fremskynde kun ved atferdsendring. Kunnskapen om denne søvnlidelsen er lav i befolkningen, men også i primærhelsetjenesten. Begrenset kunnskap fører ofte til at for eksempel foreldre og lærere ser på det forsinkede søvnmønsteret hos den unge som et resultat av kun atferds- og motivasjonelle faktorer. Over tid kan også den unge pasienten adoptere dette synet, som gjør de iboende problemene i diagnosen enda verre. Det er i tillegg mangel på evidensbaserte retningslinjer for hvordan diagnostisere, utrede og behandle DSPD.

Det første målet med denne avhandlingen var å utvikle en beskrivelse av- og utforske erfaringene til dem som lever med DSPD når det gjaldt deres daglige utfordringer og mestringsstrategier ved hjelp av individuelle dybdeintervju. Det andre målet var å studere personlighetsprofilen og andre psykologiske aspekter ved unge voksne med DSPD i en sammenligningsstudie med en gruppe friske kontroller. Det tredje målet var å studere effekten av behandling med sterkt lys og melatonin på dagtidsfungering hos pasienter med DSPD i en randomisert kontrollert studie.

I den første artikkelen rapporteres det fra en kvalitativ studie med individuelle dybdeintervju med et utvalg bestående av 9 deltakere (16-23 år) diagnostisert med DSPD. Analysene ble utført basert på systematisk tekstkondensering. Et kjernetema i alle intervjuene var hvordan håndtere ulike utfordringer relatert til lidelsen. Vi navnga de identifiserte utfordringene: 1) Å gi noe opp; 2) Å skylde på noe eller noen; og 3) Å ha et problem eller ikke. Bevissthet rundt disse utfordringene bidrar til vår forståelse av de daglige vanskelighetene til dem som har DSPD, og kan forbedre klinikerens kompetanse og evne til å hjelpe dem.

I artikkel 2 rapporteres det fra den første studien som har undersøkt NEO-Personality Inventory-Revised (NEO-PI-R)- profilen til unge voksne med DSPD. Vi

inkluderte 40 deltakere diagnostisert med DSPD (gjennomsnittlig alder 20.7) og 21 friske kontroller (gjennomsnittlig alder 21.1). Resultatene viste at unge voksne med DSPD skårte høyere på Nevrotisisme, lavere på Ekstroversjon og mye lavere på Planmessighet enn kontrollgruppen. Å vurdere personlighetsprofilen til unge voksne med DSPD før man starter behandling, kan bidra med nyttig veiledning når det gjelder hver enkelt pasient sitt behov for oppfølging.

Studien i artikkel 3 var en undersøkelse av kort- og langtidseffektene på subjektiv og objektiv søvnighet og kognitiv fungering etter behandling med sterkt lys og melatonin sammen med gradvis fremskyndede oppvåkningstider. De samme 40 pasientene med DSPD som i artikkel 2, deltok i behandlingsstudien. Fire behandlingsgrupper ble brukt i korttidsintervensjonen (to uker); placebolys + placebokapsel, sterkt lys + placebokapsel, placebolys + melatoninkapsel og sterkt lys + melatoninkapsel. Dette ble fulgt av en langtidsintervensjon (tre måneder) som inkluderte to betingelser; ikke behandling og kombinert sterkt lys + melatonin. Sammen med gradvis fremskynding av oppvåkningstid, var alle behandlingsgruppene (placebo, sterkt lys, melatonin og kombinasjonen) nesten like effektive i å bedre subjektiv søvnighet på dagtid, tretthet og kognitiv fungering i to ukers studien. Behandling med sterkt lys og melatonin reduserte subjektiv søvnighet på dagtid og tretthet og bedret kognitiv fungering i tremånedersstudien. Behandling med sterkt lys og melatonin opprettholdt og forbedret den positive effekten av behandling etter to uker, mens ikke-behandlingsgruppen gikk tilbake til baselinemål på de fleste variablene.

Oppsummert mener vi at omsorgsgivere (foreldre, psykologer, leger, sykepleiere og andre) har et bedre utgangspunkt for å hjelpe og støtte unge mennesker med DSPD hvis de har kunnskap om noen av utfordringene denne diagnosen innbefatter. Vi mener også at bevissthet rundt disse utfordringene bør tas hensyn til i fremtidig forskning på DSPD. Dette kan øke vår forståelse av de opplevde fordelene og ulempene ved å prøve å tilpasse seg et sosialt akseptert søvnmønster og andre utfordringer unge med DSPD møter, som kan påvirke de emosjonelle konsekvensene av lidelsen. Fremtidige studier er nødvendig for å utforske det kausale forholdet mellom personlighetsprofil og DSPD. Gradvis fremskynding av oppvåkningstidspunkt så ut til å være adekvat for å produsere positiv effekt på subjektiv søvnighet på dagtid, tretthet og kognitiv fungering i

korttidsbehandling av DSPD. Men, den initiale positive effekten gikk tilbake, og det ser ut til at behandling med sterkt lys og melatonin er nyttig for å opprettholde de positive effektene av behandling over tid.

Abbreviations

AAT   Alpha Attenuation Test

AAC   Alpha Attenuation Coefficient

ANOVA   Analysis of Variance

CPT-II   Conners` Continuous Performance test - II

CRSD   Circadian Rhythm Sleep Disorders

CTmin   Core body Temperature minimum

D-KEFS   Delis-Kaplan Executive Function System

DSM - IV   Diagnostic and Statistical Manual for Mental Disorders - IV

DSPD   Delayed Sleep Phase Disorder

EEG   Electroencephalography

EOG   Electrooculography

EMG   Electromyography

ESS   Epworth Sleepiness Scale

HADS   Hospital Anxiety and Depression Scale

ICD -10   International Classification of mental and behavioural Disorders - 10

ICSD - 2   International Classification of Sleep Disorders - 2

KSS   Karolinska Sleepiness Scale

MSLT   Multiple Sleep Latency Test

MWT   Maintainance of Wakefulness Test

NREM   Non-Rapid Eye Movement

PRC   Phase Response Curve

PSG   Polysomnography

RCT   Randomized Controlled Trial

REM   Rapid Eye Movement

RT   Reaction Time

SCID-I   Structures Clinical Interview for DSM-IV, Axis I diagnoses

SCN   Suprachiasmatic Nucleus

SPSS   Statistical Software Package for Social Sciences

STC   Systematic Text Condensation

SWS   Slow Wave Sleep

WAIS - III   Wechslers Adult Intelligence Scale - III

"It, like when it comes to school and stuff like that, it`s not very enjoyable [for me] to, kind of, sit there, and really want to pay attention, I mean I really want to pay attention but my eyes just cannot stay open, even if I am trying."

Participant in the study (quote from paper 1, p.54)

1. Introduction

Theoretical background for the thesis

This thesis is about Delayed Sleep Phase Disorder (DSPD) in adolescence and young adulthood. Sleep problems are common in adolescence (Crowley et al. 2007) and adolescents consistently get inadequate amounts of sleep (Smaldone et al. 2007) and the tendency to delay bedtimes by more than 2 hours during weekends is seen worldwide (Gradisar et al. 2011b). Such a delayed sleep pattern is similar to symptoms of DSPD, which is a circadian rhythm sleep disorder (CRSD) where the sleep period is delayed with respect to conventional norms (American Academy of Sleep Medicine 2005). Those who fulfil the criteria for DSPD however, have a more rigid circadian rhythm delay which is assumed to be difficult or impossible to advance by behavioural means only (American Academy of Sleep Medicine 2005). DSPD comprises complaints of excessive daytime sleepiness and impairments in daytime functioning and quality of life (Bjorvatn and Pallesen 2009; Crowley et al. 2007; Nagtegaal et al. 2000). People with DSPD are commonly misdiagnosed with sleep onset insomnia (American Academy of Sleep Medicine 2005). The knowledge about DSPD is scarce in the general population (i.e. parents and teachers) as well as in primary health care settings (Wyatt 2004). This lack of knowledge leads for example parents and teachers of young patients with DSPD to attribute the sleep-wake problems to motivational and behavioural factors (Dagan and Eisenstein 1999), which consequently might result in inter-relational problems. Over time, the patient might adopt this concept, which adds to the problems innate in the diagnosis (Dagan 2002). There is also a lack of evidence-based guidelines regarding how to diagnose, examine and treat circadian rhythm sleep disorders (Sack et al. 2007). The overall aim of this thesis was to gain new evidence-based knowledge about DSPD in order to be able to understand and help patients better. The first specific aim of this thesis was to explore and develop descriptions of the experiences of patients diagnosed with DSPD regarding their daily challenges and coping mechanisms, by individual in-depth interviews. The second aim was to investigate the personality profile and other psychological aspects of patients with DSPD in a comparative study with healthy controls. The third aim was to assess the effect of treatment with bright light and

melatonin on daytime function in patients with DSPD in a randomized controlled trial (RCT). An introduction to sleep regulation mechanisms and a short overview of the current knowledge about DSPD will be presented before the presentation of the study.

1.1 Sleep and sleep regulation

Sleep

Sleep can be defined as "a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment" (Carskadon and Dement 2011). The gold standard of measuring sleep is by polysomnography (PSG), which comprises electroencephalography (EEG/brain waves), electrooculography (EOG/eye movements) and electromyography (EMG/muscle activity) (Keenan and Hirshkowitz 2011). Sleep has two main separate physiological states; non-rapid eye movement (NREM) and rapid-eye movement (REM), which alternate cyclically across a sleep period. A normal night`s sleep period comprises of 4-6 sleep cycles of approximately 90 minutes each (ranging from 70 to 120 minutes) (Carskadon and Dement 2011). NREM sleep is normally further divided into three stages (stage N1, N2 and N3) (Keenan and Hirshkowitz 2011). The sleep stages refer to what we may call the "depth" of sleep; N1 refers to "light sleep" and is a borderline stage between wakefulness and sleep. Wakefulness is mainly represented physiologically by high-frequency (>17 Hz; beta range), low voltage EEG patterns. EEG patterns in stage N1 sleep are of relatively low-voltage (5-7 Hz; theta activity), mixed frequency activity and represent about 5% of the total sleep time (Keenan and Hirshkowitz 2011). N2 also refers to relatively low voltage patterns (theta), mixed frequency but also includes sleep spindles and K-complexes. N2 is seen across all sleep cycles throughout the sleep period, and about 50% of the total sleep time is spent in this stage in healthy young adults (Keenan and Hirshkowitz 2011). EEG patterns in N3 are of high amplitude waves in the low frequency range (<4 Hz; delta range) (Keenan and Hirshkowitz 2011). Because of the low frequency waves (especially delta waves occurring at the low end of the frequency spectrum; ≤2 Hz), N3 sleep is often referred to as slow wave sleep (SWS). We have a much higher threshold for waking up from N3

than from N2 and N1. Approximately 12.5-25% of the sleep period in adults is spent in N3 (Keenan and Hirshkowitz 2011). REM sleep is defined by relatively low voltage, mixed frequency EEG waves with simultaneous rapid eye movements and muscle atonia (Carskadon and Dement 2011). The majority of N3 sleep takes place during the first half of the sleep period, while the majority of REM sleep happens during the second half of the sleep period (Carskadon and Dement 2011).

Sleep regulation

Sleep is regulated in interplay between three factors: the homeostatic factor; the circadian factor and behaviour/habits (Bjorvatn and Pallesen 2009). The homeostatic factor represents a sleep propensity which is accumulated during wake time; hence the longer you go without sleep, the more the propensity to sleep will increase (Banks and Dinges 2007; Borbély et al. 1981). This propensity to sleep is particularly important for the amount of N3 sleep. N3 sleep is considered the best restorative sleep and hence the most important in order to feel alert after sleep. Our circadian rhythm makes it easy to sleep at certain periods of the 24-hour day, for most people at night time. The circadian factor is particularly important for sleep length, and is the reason that we sleep shorter on a day after for example a night shift than we usually would during a normal night (Bjorvatn and Pallesen 2009; Czeisler and Dijk 1995; Czeisler et al. 1980). In addition to these two biological factors, our habits and behaviours play an important role in sleep regulation. This factor explains how we can stay awake during i.e. night work or a social situation such as a party, when both the homeostatic and the circadian factors would promote sleep. One can override the two former factors for sleep regulation by engaging in activities that promote alertness, such as drinking coffee, interacting with others socially or over the internet/mobile phones, increased illumination and so on (Bjorvatn and Pallesen 2009; Carskadon et al. 2004).

1.2 Circadian rhythms

A circadian rhythm (circa = about, dias = day) can be seen in many bodily functions (i.e. hormone secretion) and is governed by the suprachiasmatic nuclei (SCN) in the hypothalamus (Turek 2011). The length of the endogenous rhythm of the SCN is normally somewhat longer than 24 hours (Czeisler and Gooley 2007), but external stimuli usually adjust this rhythm to the length of a day; 24 hours. The circadian rhythm of core body temperature and the secretion of melatonin are commonly used as markers of the human circadian phase (Burgess et al. 2002). Body temperature varies with almost one degree Celsius through a day and night, and core body temperature minimum (nadir) will from now on in the thesis be referred to as CTmin (see illustration in Figure 1). The SCN is considered to be at the top of the hierarchy of the mammal circadian clock system (Turek 2011).
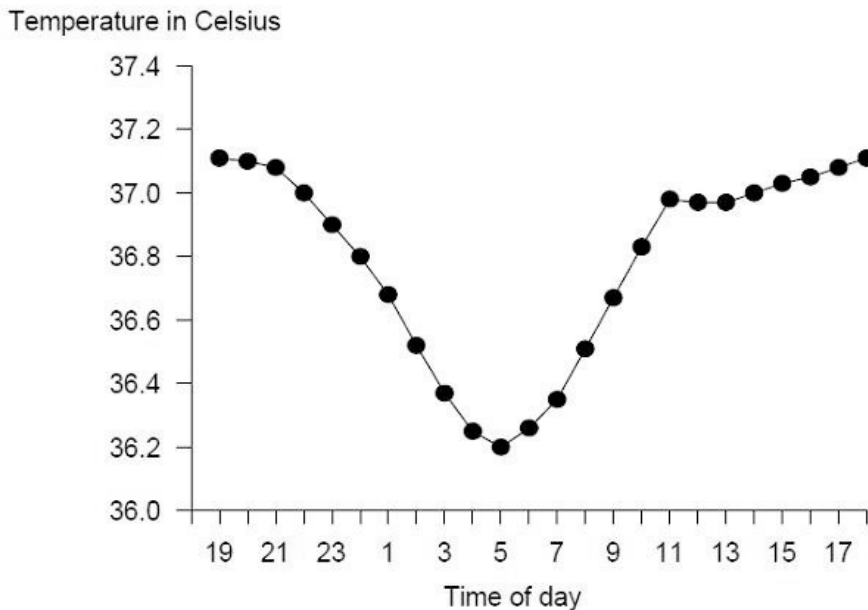

Figure 1. Core body temperature rhythm in a person with habitual sleep time between 11pm and 7am (from Bjorvatn & Pallesen, 2009).

Entrainment of the circadian rhythm by light and melatonin

Light is the most important rhythm modulator (Czeisler et al. 1989) and has impact on the SCN via neuronal connections projecting from the retina (the retinohypothalamic tract). The effect of light follows a phase-response curve (PRC) (Khalsa et al. 2003) where light prior to CTmin delays, and light after CTmin advances the circadian rhythm (Bjorvatn and Pallesen 2009; Dijk et al. 1995). CTmin occurs usually 1-2 hours before habitual time of awakening (see Figure 1). In addition, light exposure close to CTmin has the greatest phase shifting effect, hence light in the middle of the day or temporally far from CTmin has little phase-shifting properties.

The SCN projects to the pineal gland where production and release of melatonin are stimulated by darkness and suppressed by light, about 12 hours out of phase with the PRC to light (Lewy et al. 1998). Our ability to sleep is normally low in the late morning and increases in the evening probably due to the secretion of melatonin during the darkness of the evening. Melatonin is also involved in regulating the circadian rhythm of several other physiological processes. Melatonin follows (together with hormones such as for example cortisol and adrenocorticotropic hormone (ACTH)) a circadian rhythm of secretion in healthy subjects (Guardiola-Lemaître and Quera-Salva 2011).

Individual differences in circadian rhythms

Individual preference for timing of activities such as work, exercise and sleep is often referred to as type A or B people, or morning "larks" and evening "owls". Morning types have earlier body temperature peak than evening types, whereas the intermediate type has body temperatures between those of the other groups (Horne and Östberg 1976). Although morningness-eveningness differences do not seem to induce differences in sleep duration, evening types have a delayed sleep period compared with morning types; they retire to bed later and rise later. Morningness-eveningness is a dimension where the majority of the population is "intermediate type". In a large university student population, approximately 16% were morning types, 60% intermediate types and 24% evening types (Adan and Natale 2002). Following young adult age there is an age-related shift towards morningness; hence more adolescents and young adults are evening types than in older

populations (Adan et al. 2012). In a review on the cognitive parameters of morning and evening types, it is suggested that diurnal preference is not only related to behaviour, but also to various functions that influence personality organization (Cavallera et al. 2011). In another recent review on circadian typology, it is suggested that the lifestyle of the evening type is a risk factor for some disorders, while the patterns of the morning type is a protective factor (Adan et al. 2012).

1.3 Adolescence and young adulthood

Sleep in adolescence

Adolescent sleep habits seem to show a pattern of delayed bed times and decreased total sleep time (Carskadon 1990), particularly during weekdays. Research has shown that adolescents do not have a decreased need for sleep, but in actuality, have an increased need for sleep compared to pre-pubertal sleep need (Carskadon 1990). Puberty in itself seems to impose increased daytime sleepiness in healthy adolescents unrelated to length of sleep (Carskadon et al. 1980), and parental involvement in boundaries and bed times fade during this time (Carskadon 1990). A biological delay in the sleep period is normal during adolescence (Carskadon et al. 1993). A recent review and meta-analysis of sleep patterns and problems during adolescence, shows that adolescents typically get insufficient total sleep time during school-nights (Gradisar et al. 2011b). Sleep restriction over time causes neurobiological deficiencies in the ability to be alert and cognitive performance decrements (Banks and Dinges 2007). Accumulated sleep restriction has shown to have a dose-response cost on neurobehavioral functions (Van Dongen et al. 2003). Consequences of chronic insufficient sleep/sleep curtailment can be summed up to: daytime sleepiness; vulnerability to accidents; mood and behavioural problems; increased tendency to abuse drugs and alcohol; reduced school performance; and increased probability to develop sleep disorders (Carskadon 1990; Gradisar et al. 2011b; Saxvig et al. 2012).

Psychological development in adolescence and young adulthood

Puberty, adolescence and young adulthood are periods of huge transitions bodily, physiologically as well as psychologically. One of the main developmental tasks in adolescence and young adulthood is to navigate the transition from their family towards stronger reliance on peer relations and romantic relations (Kroger 2000). Good interpersonal relations and a healthy sense of self-regard may increase resilience towards problems later in life, such as mood disturbances and other problems (Kroger 2000). Circadian rhythms affect many physiological, psychological and social dimensions of our lives (Dagan et al. 1996). In terms of morningness, several studies have linked this to other prominent personality traits (Tankova et al. 1994; Tsaousis 2010). A meta-analysis and a large review showed that conscientiousness (relating to organized behavior) was the one dimension most positively related to morningness, while agreeableness (relating to altruistic behavior) was also positively related to morningness, but to a lesser degree (Adan et al. 2012; Tsaousis 2010). Based on longitudinal studies, it has been suggested that the greatest changes in personality traits are found in younger populations (Roberts et al. 2006; Srivastava et al. 2003).

1.4 Delayed sleep phase disorder

Definition and diagnosis

Several disorders have been described involving a disruption of the circadian rhythm. DSPD was first described in 1981 by Weitzman and colleagues (Weitzman et al. 1981) as a "chronobiological disorder with sleep onset insomnia". According to the International Classification of Mental and Behavioural Disorders, 10th version (ICD-10) (World Health Organization 1992), circadian rhythm sleep disorders are defined as "a lack of synchrony between the individuals´ sleep – wake schedule and the desired sleep – wake schedule for the environment, resulting in a complaint of insomnia or hypersomnia" (p. 183). A similar description is found in the Diagnostic and Statistical Manual of Mental Disorders-IV (4th edition) (DSM-IV) (American Psychiatric Association 1994). The

most elaborated diagnostic system on sleep disorders is the International Classification of Sleep Disorders, second version (ICSD-2) (American Academy of Sleep Medicine 2005). CRSD`s are divided into nine categories; Delayed sleep phase disorder, Advanced sleep phase disorder, Irregular sleep-wake rhythm, Nonentrained type, Jet lag disorder, Shift work disorder, CRSD due to medical condition, other CRSD not otherwise specified; and other CRSD due to drug or substance. Table 1 shows the diagnostic criteria for DSPD.

Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type

(Delayed Sleep Phase Disorder)

A. There is 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 desired and socially acceptable time.

B. When allowed to choose their preferred schedule, patients will exhibit normal sleep quality and duration for age and maintain a delayed, but stable, phase of entrainment to the 24-hour sleep-wake pattern.

C. Sleep log or actigraphy monitoring (including sleep diary) for at least seven days demonstrates a stable delay in the timing of the habitual sleep period.

Note: In addition, a delay in the timing of other circadian rhythms, such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the delayed phase.

D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Table 1. Diagnostic criteria for DSPD adapted from the ICSD-2 (American Academy of Sleep Medicine 2005).

DSPD does not involve a dysfunction of the sleep period itself, but simply a delay of the circadian rhythm (Saxvig et al. 2013b; Thorpy et al. 1988; Weitzman et al. 1981). Thus, patients with DSPD have problems initiating sleep if they go to bed at a conventional time and they accordingly experience severe sleepiness during morning hours (American Academy of Sleep Medicine 2005; Thorpy et al. 1988; Weitzman et al. 1981).

Prevalence

DSPD is probably the most prevalent of the CRSD`s and is most common among adolescents and young adults. Few prevalence studies have used the diagnostic criteria

according to the ICSD-2, and prevalence rates have accordingly showed large variations. Prevalence rates from 0.13% to 16.6% have been reported (Brown et al. 2001; Hazama et al. 2008; Lack 1986; Ohayon et al. 2000; Saxvig et al. 2012; Schrader et al. 1993; Yazaki et al. 1999). According to the ICSD-2, the prevalence of DSPD in adolescence and young adulthood is between 7% and 16% (American Academy of Sleep Medicine 2005).

1.4.1 Aetiology

There are various hypotheses concerning the pathophysiology of DSPD based on biological and psychosocial factors (Carskadon et al. 1993; Crowley et al. 2007; Wolfson and Carskadon 1998), however the aetiology is still mainly unknown (Sack et al. 2007). It has been proposed that DSPD may be partially due to a genetic disposition or risk factor, as polymorphism in the promoter of the clock gene *PER3* could change its expression, leading to potential differences in the observed functions (Archer et al. 2010). Reduced sensitivity to daytime light and increased sensitivity to evening light have been proposed as aetiological reasons for DSPD, supported by for example Aoki and colleagues (Aoki et al. 2001), who found more pronounced suppression of nocturnal melatonin secretion by light in patients with DSPD.

It has been suggested that patients with DSPD have difficulties adjusting or entraining their rhythm (Uchiyama et al. 1999). This may suggest either a reduced accumulation of the homeostatic factor during time awake, or a reduced ability to alleviate the homeostatic factor when allowed to sleep. Some researchers have also proposed that patients with DSPD have a longer phase angle relationship between endogenous circadian rhythm and sleep (i.e. misalignment of the CTmin in relation to sleep onset and/or sleep offset) (Campbell and Murphy 2007; Ozaki et al. 1996; Uchiyama et al. 2000; Uchiyama et al. 1992; Watanabe et al. 2003). Furthermore, extremely long endogenous rhythms have been proposed as the biological aetiology for DSPD (Campbell and Murphy 2007), but this has also been contradicted (Chang et al. 2009; Wyatt et al. 2006).

Some might describe patients with DSPD as extreme evening types on the morningness-eveningness preference continuum. However, Abe and colleagues (Abe et

al. 2011) found that patients diagnosed with DSPD according to ICSD-2 criteria, may be both "moderate evening types" and "intermediate types", not only "extreme evening types" as one might expect. Hence, the notion that patients with DSPD simply are extreme evening types seems unlikely. Dagan and Eisenstein (1999) describe DSPD patients` circadian rhythm as more rigid than extreme evening types without DSPD. Also, extreme evening types do not all have DSPD; hence there seem to be something qualitatively different about the underlying aetiology. Dagan and colleagues (1998) have found DSPD to be more prevalent in a psychiatric population of patients with personality disorders than in patients with axis I diagnoses. They suggest that the idiosyncrasies in the sleep-wake rhythm of patients with DSPD may be comparable to the features of personality disorders in that both diagnoses are based on a deviation from the norm in the culture/society (Dagan et al. 1998a).

Another aspect of the aetiology of DSPD, is that this patient group seems to be heterogeneous (Regestein and Pavlova 1995), which might be one of the reasons a consensus about the pathophysiology is difficult to reach. Regardless of the path to the development of DSPD, psychological and behavioural factors seem to be important contributors (Lack and Wright 2007). Bad sleep habits/poor sleep hygiene such as staying up late even though feeling tired, may exaggerate the symptoms of DSPD and probably also trigger an underlying predisposition (Pelayo et al. 1988; Regestein and Pavlova 1995). On the other hand, many patients with DSPD feel alert and energetic in the evening (as indicated by their evening preference) and appreciate this time too much to want to cut it short (Lack and Wright 2007). These factors are probably valuable to address in treatment of DSPD.

1.4.2 Comorbidity and psychological characteristics

Patients suffering from DSPD are often required to rise early in the morning in order to adhere to domestic, school or job obligations. Due to late sleep onset, chronic sleep loss is a common consequence and many patients with DSPD are often unable to meet at school/work early in the morning. DSPD has accordingly been associated with poor academic achievement and academic failure (Dagan et al. 1998a; Gradisar et al. 2011a;

Sack et al. 2007; Saxvig et al. 2012), increased alcohol and substance abuse (Saxvig et al. 2012), elevated symptoms of anxiety and depression (Regestein and Pavlova 1995; Saxvig et al. 2012; Weitzman et al. 1981) and comorbidity with other conditions such as hypochondria (Regestein and Monk 1995; Thorpy et al. 1988), affective disorders (Abe et al. 2011; Lewy 2009), attention disorders (Gruber et al. 2007), learning disorders, and personality disorders (Dagan and Eisenstein 1999; Dagan et al. 1996; Regestein and Pavlova 1995; Shirayama et al. 2003). DSPD patients have also been found to have reduced quality of life (Nagtegaal et al. 2000).

Very few studies have addressed the personality profile of patients with DSPD. It is reported that patients with DSPD have elevated scores on some of the clinical subscales on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Alvarez et al. 1992; Shirayama et al. 2003; Takahashi et al. 2000; Wyatt 2004). The MMPI-2 is developed to measure pathological personality profiles (Butcher 2010). The "Big Five" (also know as the five factor model) of "normal personality" is one of the most widely recognized personality models (Wiggins and Trobst 1997) and comprise five dimensions: Neuroticism (adjustment or emotional stability versus maladjustment and nervousness), Extroversion (active and sociable versus reserved and even-paced), Openness to experience (imaginative and intellectually oriented versus conventional and closed), Agreeableness (altruistic and sympathetic versus egocentric and competitive) and Conscientiousness (organized and reliable versus disorganized and lackadaisical) (Costa and McCrae 1992). The Big Five model has been validated across several cultures (McCrae et al. 1998). To our knowledge, no previous study has investigated the Big Five personality profile of patients with DSPD. However, there is a magnitude of research on the relationship between circadian preferences in healthy people and personality traits (Adan et al. 2012; Muro et al. 2009; Tonetti et al. 2009; Tsaousis 2010). The most consistent finding is that morningness is associated with high scores on Conscientiousness (Adan et al. 2012; Tsaousis 2010).

Compliance with treatment regimens is often considered problematic in patients with DSPD (Carskadon et al. 1993; Gradisar et al. 2011a; Regestein and Pavlova 1995; Sack et al. 2007), and many patients with DSPD seem to drop out of school and treatment studies (Gradisar et al. 2011a; Regestein and Pavlova 1995). Several researchers suggest

that treatment plans for some patients with DSPD should address motivation and willingness to persist (Alvarez et al. 1992; Gradisar et al. 2011a; Regestein and Pavlova 1995). Assessing the personality profile of patients with DSPD might be one way of addressing psychological characteristics related to motivation and treatment compliance.

Research on DSPD has primarily focused on sleep and the underlying circadian rhythm. Thus, knowledge about how DSPD might affect self-image and perceived interpersonal relationships is lacking. In the perspective of the psychological developmental tasks one is faced with in adolescence and young adulthood, it seems of great importance to investigate the psychosocial characteristics related to DSPD.

1.4.3 Daytime function and sleepiness

The tendency to unintentionally doze off during the day at school or work is a common symptom of patients who come to sleep specialist centres (Johns 1998). A sleepy person tends to show impaired function (Banks and Dinges 2007; Bonnet et al. 2005). As the brain becomes sleepier, the more the subjects` responses will be influenced (Dinges et al. 1987). Practitioners of sleep medicine are according to Johns (1998) not able to quantify sleepiness routinely, and there seem to be confusion about the semantics when discussing "daytime sleepiness" (Horne 2010; Johns 1998). Drowsiness, hypersomnia, somnolence, sleep propensity, fatigue, tiredness, the ability to fall asleep, sleep ability, the ability to stay awake, subjective sleepiness, objective sleepiness and manifest sleepiness are all used to describe the phenomenon of "daytime sleepiness" (Johns 1998). Horne (2010) discusses the matter of what sleepiness is, and how it is related to sleep debt or a need to sleep. Horne further questions in his recent review on sleepiness, whether "sleepiness", "the propensity to fall asleep" and "need for sleep" are qualitatively different (Horne 2010).

Since the sleep period is delayed in patients with DSPD, they have more SWS between 6am and 8am than controls (Saxvig et al. 2013b). This is the time many have to rise in order to be in time for school or work obligations. Sleep curtailment typically leads the patients to catch up on sleep when they can, i.e. by napping and by extending sleep on weekends and holidays, which only maintain and potentially increase the sleep

phase delay the following nights (Crowley et al. 2007). It is likely then, that sleepiness in patients with DSPD can be due to several factors; the point of time of their endogenous circadian rhythm, sleep curtailment (sleep debt), and sleep deprivation over time (chronic sleep deprivation).

Sleepiness can be assessed by i) self-evaluations (subjective sleepiness), ii) physiological measures such as sleep propensity and/or arousal decrease (objective sleepiness) and iii) performance on behavioral tests (cognitive function) (Curcio et al. 2001). Subjective measures and behavioral measures have been considered to be influenced by motivational confounding variables, whereas physiological measures such as spectral power of EEG bands has been considered to be less influenced by such variables. It has been reported that the increase in EEG power density in the theta-alpha frequencies accumulated during extended wakefulness, probably is associated with a homeostatic sleep propensity increase (Cajochen et al. 1995, 2000).

Self-evaluations of subjective sleepiness

Subjective self-evaluations of sleepiness are widely used in sleep research. Common sleepiness scales are the Karolinska Sleepiness Scale (KSS) (Åkerstedt and Gillberg 1990) and the Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973; Horne 2010). These tests are rated on a 9- and a 7-point Likert-like scale (1-9 for the KSS and 1-7 for the SSS) where the participant rates their concurrent level of perceived subjective alertness/sleepiness. Another widely used self-evaluation measure of sleepiness (dozing behavior) is the Epworth Sleepiness Scale (ESS) (Johns 1991), which is a measure of trait sleepiness, referring to a general tendency to doze off/fall asleep in different situations. ESS comprises 8 questions, all rated on a 4-point scale (0-3).

Physiological measures of objective sleepiness (sleep propensity and/or arousal decrease)

The most widely used physiological measure of sleep propensity is the Multiple Sleep Latency Test (MSLT) developed by Carskadon and Dement (Carskadon et al. 1986). Short average sleep latency is considered to reflect a high sleep propensity (Carskadon et al. 1986). The MSLT is costly and time-consuming and requires a trained polysomnographer. Also, inter-rater variability may be a methodological challenge with the MSLT, as well as individual differences in the ability to fall asleep regardless of the underlying physiological sleep propensity (Stampi 1995). The Alpha Attenuation Test (ATT) is a test measuring physiological arousal and was developed based on the fact that EEG power spectrum in the alpha frequency band increases with open eyes and decreases with eyes closed as the subject becomes sleepier (Stampi 1995). In contrast to MSLT, scoring does not require a trained polysomnographer, it does not require a sleep-conducive environment, it is less disruptive on the subjects` state and can be applied quite easily in the field or in the laboratory (Stampi 1995).

Performance on behavioural tests (cognitive function)

Neurobehavioural tests of sustained attention are i.e. the Psychomotor Vigilance Test (PVT) (Dinges and Powell 1985) (measuring behavioural alertness) and the more recent Conners` Continuous Performance Test – II (CPT-II) (Conners and MHS Staff 2004) (measuring different aspects of attention). Wechslers` intelligence tests are the most widely used intelligence tests (Tulsky and Ledbetter 2000), and subtests of the Wechslers` Adult Intelligence Scale – III (WAIS-III) (Wechsler 1997) can be used to assess different cognitive modalities (working memory, processing speed, executive function etc.). The Delis-Kaplan Executive Function System (D-KEFS) (Delis et al. 2001) measures more basic functions as well as more demanding ones to assess key components of executive functioning.

Tests of sustained attention such as the PVT are considered sensitive to sleepiness levels (Van Dongen et al. 2003), whereas tests of executive functions seem to require

long periods of wakefulness in healthy subjects, in order to show subtle differences in sleepiness (Horne 2010). Although the effect of sleep deprivation is known to affect cognitive function in healthy subjects, little is known about how this influence patients with DSPD. Recently, Shekleton and colleagues (2010) reviewed studies on neurobehavioral performance in patients with insomnia. The most consistent impairments were shown on tests of different aspects of attention and executive function, and their results called for the inclusion of standard psychometric tests in future studies of different sleep disorders (Shekleton et al. 2010).

Sleepiness appears to be a multidimensional phenomenon where sleepiness states are qualitatively distinct and are influenced by different mechanisms (Franzen et al. 2008; Horne 2010; Stampi 1995; Van Dongen et al. 2003). To assess sleepiness and treatment effects in patients with DSPD, in the absence of a consensus on the definition of sleepiness, it seems important to assess a wide range of measures believed to be influenced by subjective sleepiness.

1.4.4 Treatment

Historically, chronotherapy (a daily 3-hour delay of the sleep period each day until conventional rise and sleep times are reached) was the first treatment option for DSPD (Weitzman et al. 1981). Today, timed bright light exposure and melatonin administration are the most widely used treatment options for DSPD in clinical practice (Barion and Zee 2007; Bjorvatn and Pallesen 2009; Lack and Wright 2007).

Bright light treatment

The timing of light is crucial (Bjorvatn and Pallesen 2009) as light before core body temperature minimum (CTmin) delays the circadian rhythm, whereas light after CTmin advances the circadian rhythm (Khalsa et al. 2003). The issue of light intensity, effects of different wavelengths and the timing of light treatment is under debate in the research literature (Lack and Wright 2007). Short wavelength light has proven more effective on

phase-advancing human circadian rhythms than the broad spectrum white light (Warman et al. 2003; Wright et al. 2004). However, the safety of short wavelength light and especially blue spectrum light is unclear (Lack and Wright 2007). Full spectrum (white) light is the most commonly used light treatment.

Bright light in the morning or after awakening has proven to be effective in advancing the sleep phase in patients with DSPD (Lack et al. 2007; Rosenthal et al. 1990). Lack and colleagues (2007) used blue light LED masks and found advances of the sleep phase after 1 week of treatment; however they did not assess measures of daytime function. Rosenthal and colleagues (1990) conducted the only study that we know of on patients with DSPD assessing the effects of bright light treatment on objective sleepiness (sleep propensity) by the multiple sleep latency test (MSLT). Their bright light group (2500 lux) showed increased sleep latency at 9am and 11am (but not at other times during the day) compared to the dim light group (300 lux). Cole and colleagues (2002) found reduced subjective morning sleepiness in a bright light group (2700 lux masks) compared to a dim light group (<0.01 lux masks) but only in the most delayed subjects (Cole et al. 2002). Recently, cognitive behavioural therapy in combination with bright light therapy showed promising effects on advancement of the sleep period, subjective sleepiness and fatigue in adolescents with DSPD (Gradisar et al. 2011a). Cognitive behavioral therapy involves (among other aspects) psychoeducation and aims to challenge destructive thoughts and patterns of interpretation and work on alternative, more helpful thoughts and interpretations. This will most likely reduce negative affect. Side-effects of bright light are usually not serious and of short duration (Wyatt 2004). Bright light treatment is a relatively complex and time-comsuming treatment. Typically, it is advised to be exposed to 10 000 lux full-spectrum light for 30 minutes to achieve the wanted phase-advancing effects (Terman and Terman 2011). A clinical advantage of bright light can be an immediate effect as many feel alerted by the bright light similar to the feeling of sunlight reaching the eyes.

Exogenous melatonin treatment

Exogenous melatonin administration also follows a phase-response curve (Dahlitz et al. 1991; Lewy et al. 1998). The phase advancing effect of melatonin seems to be somewhat better documented than the phase delaying effect (Arendt 2000). In clinical practice it has been recommended to administer melatonin 5-7 hrs before the regular time for sleep onset in order to obtain maximal phase advance (Lewy et al. 1998; Mundey et al. 2005). Accordingly, studies on DSPD have shown that the sleep period may be advanced by use of melatonin in the evening, usually taken a few hours before sleep onset (Dahlitz et al. 1991; Kayumov et al. 2001; Mundey et al. 2005; Nagtegaal et al. 1998; Rahman et al. 2010). Comparing melatonin studies is difficult because the treatment protocols have varied regarding timing of treatment and dosage, but melatonin treatment seems to be effective in the treatment of DSPD according to a recent review (van Geijlswijk et al. 2010). Mundey and colleagues (2005) found differences in phase-advancing effects depending on the timing of the melatonin treatment on a 28-day schedule. Administration 6 hours before baseline DLMO yielded a larger phase-advance than administration of melatonin 1 to 3 hours before baseline DLMO. Only two of the aforementioned studies included measures of subjective daytime sleepiness/alertness. Dahlitz and colleagues (1991) found no changes on self-reported alertness. Kayumov and colleagues (2001) found no overall difference in measures of subjective sleepiness, fatigue and alertness between a melatonin and a placebo group. However, when adhering to an imposed sleep schedule (midnight to 8am), subjects taking melatonin were less sleepy and fatigued than the placebo group. The advantage of melatonin treatment compared to light treatment is that it is relatively simple to administer. Melatonin generally gives few serious side-effects and seems to be tolerated well by most patients, however there is a lack of long-term studies and we know little about possible drug interactions (Bjorvatn and Pallesen 2009).

Combination of bright light and melatonin

The combination of treatment with bright light in the morning and melatonin in the evening, has shown greater phase-advance effects than the effect of morning bright light alone (Revell et al. 2006; Wirz-Justice et al. 2004). This suggests that the effect of melatonin in the evening is additive to the effects of bright light in the morning (Lack and Wright 2007), and the combination seems to reduce the circadian misalignment often seen while administering melatonin only (Crowley and Eastman 2013).

Timing of treatment

Because the magnitude of treatment effect varies with the timing of light and the timing of melatonin treatment, measuring circadian markers such as DLMO and/or CTmin before initiating treatment seem preferable. However, measuring DLMO and/or CTmin are invasive and costly procedures that are difficult to implement in clinical practice. In assessment of circadian phase timing, spontaneous wake-time after self-chosen sleep periods is informative (Lack and Wright 2007). Good sleepers who slept at self-chosen times rather than imposed sleep times, have shown high correlations between DLMO and wake time (Burgess and Eastman 2005). Hence, starting bright light treatment immediately after spontaneous awakening on the first day of treatment (preferably after a few days of self-chosen sleep schedules) and then gradually advance light exposure by 30 up to 60 minutes each day until target rise time is reached, has been recommended and proven effective (Bjorvatn and Pallesen 2009; Gradisar et al. 2011a).

Short- and long-term treatment for DSPD

There is currently not sufficient empirical evidence to recommend specific treatment guidelines for DSPD (Barion and Zee 2007; Bjorvatn and Pallesen 2009; Gradisar et al. 2011a). Despite the fact that DSPD is most common in adolescence and young adulthood, we only know of one treatment study on adolescents with DSPD (Gradisar et al. 2011a). Hence, there is still a great need for further well-controlled empirical studies

that investigate the effects of bright light and exogenous melatonin in patients with DSPD. Long-term studies are non-existing in the research literature.

Participant: "Yes, it is, it affects me a lot psychologically sort of, it is like, if I go to bed now then I cannot sleep, then I might as well be awake. And then that results in problems the rest of the day and then, I maybe become grumpy and then, yes."

Interviewer: "(…) when you say it affects you a lot psychologically, what do you mean by that?"

Participant: "I don't really know, I just know that there is something in me in a way, I know that it won`t work and then, I sort of just give up."

Participant in the study (quote from paper 1, p. 55)

2. Research aims

Paper 1

The aim of paper 1 was to explore the phenomenological understanding and description of the informants` experiences of their life world with DSPD. We set up a qualitative study with adolescents and young adults diagnosed with DSPD, exploring their daily challenges and coping mechanisms, using individual in-depth interviews.

Paper 2

The main aim of paper 2 was to investigate the NEO-PI-R personality profile of patients with DSPD in a comparative study with healthy controls. The second aim of paper 2 was to compare psychological aspects (intelligence, school grades, subjective health complaints, fatigue, symptoms of anxiety and depression, symptoms of insomnia, sleepiness and sleep quality) between the two groups.

Paper 3

The main aim of paper 3 was to assess the effect of bright light and melatonin treatment on subjective and objective sleepiness in patients with DSPD. The second aim was to investigate the effect of the same treatment on cognitive functions. We investigated the short-term (two weeks) effect of bright light and melatonin treatment in a randomized, four-armed, double blinded, placebo controlled trial (RCT). We investigated long-term (approximately three months) effects of combined bright light and melatonin treatment in a randomized, two-armed follow-up trial.

3. Methods

All papers in this thesis stem from one large case-control/clinical trial study with the same participants. An overview of the study, the participants and the instruments used will be presented before presenting the procedures for each paper separately.

3.1 Overview of the study

3.1.1 Participants

The participants were recruited through advertisements at high schools, a college and a university (i.e. e-mails, flyers, posters and stands). Participants in the DSPD-group were recruited to take part in a randomized controlled trial (RCT) (ClinicalTrials.gov Identifier: NCT00834886) with bright light therapy and melatonin administration. Participants in the control group were recruited to take part in a comparative study on sleep and daytime functioning. The three studies reported here are parts of a larger study protocol.

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

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

A total of 319 potential participants took initial contact, 264 for the DSPD-group and 55 for the control-group. In total, 60 persons fulfilled the basic criteria for inclusion in the DSPD-group, 31 for the control-group, and were scheduled for a meeting. Of the 60 in the DSPD-group, 10 withdrew prior to the scheduled meeting. The remaining 50 plus 31 (in total 81) potential participants were screened with the Structured Clinical Interview for DSM-IV diagnosis (SCID-I) (First et al. 1997), the IQ test Raven`s Progressive Matrices (Raven 2000) and pregnancy test (only females) and further set up for a polysomnographic screening (PSG). A total of 40 participants were included and randomized for participation in the DSPD-group and 21 in the control-group (see Figure 2 and 3 for withdrawal/exclusion categories). Neither of the participants had ever before been diagnosed with DSPD nor had they at any time previously received treatment for DSPD. Inclusion and data collection were performed from the fall of 2008 until early 2012. All meetings with participants took place at the sleep laboratory at the Faculty of Psychology, University of Bergen. Figure 2 and 3 illustrate the participant flow throughout the study.
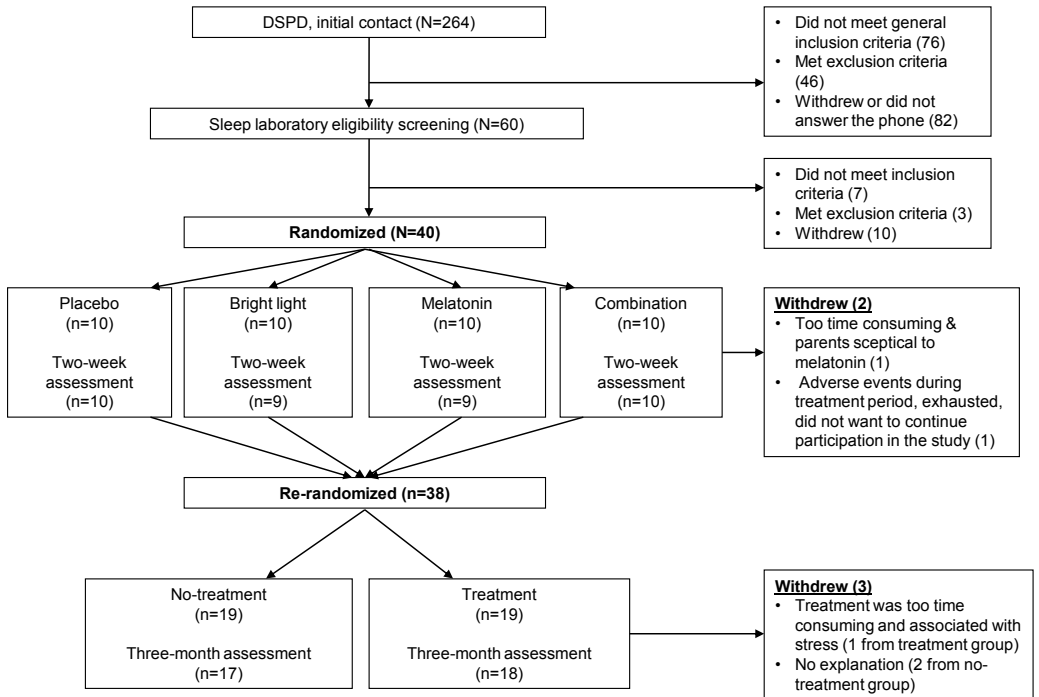
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┌─────────────────────────────────────┐          ┌──────────────────────────────┐
│   DSPD, initial contact (N=264)     │          │ • Did not meet general       │
└─────────────────────────────────────┘          │   inclusion criteria (76)    │
                   │                              │ • Met exclusion criteria     │
                   │──────────────────────────▶   │   (46)                       │
                   ▼                              │ • Withdrew or did not        │
┌─────────────────────────────────────┐          │   answer the phone (82)      │
│ Sleep laboratory eligibility        │          └──────────────────────────────┘
│ screening (N=60)                    │
└─────────────────────────────────────┘          ┌──────────────────────────────┐
                   │                              │ • Did not meet inclusion     │
                   │──────────────────────────▶   │   criteria (7)               │
                   ▼                              │ • Met exclusion criteria (3) │
┌─────────────────────────────────────┐          │ • Withdrew (10)              │
│        Randomized (N=40)            │          └──────────────────────────────┘
└─────────────────────────────────────┘
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Placebo (n=10) Two-week assessment (n=10)	Bright light (n=10) Two-week assessment (n=9)	Melatonin (n=10) Two-week assessment (n=9)	Combination (n=10) Two-week assessment (n=10)

Withdrew (2)
• Too time consuming & parents sceptical to melatonin (1)
• Adverse events during treatment period, exhausted, did not want to continue participation in the study (1)

Re-randomized (n=38)

No-treatment (n=19) Three-month assessment (n=17)	Treatment (n=19) Three-month assessment (n=18)

Withdrew (3)
• Treatment was too time consuming and associated with stress (1 from treatment group)
• No explanation (2 from no-treatment group)

Figure 2. Participant flow in the study, DSPD-group.

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                    ┌──────────────────────────────────────┐
                    │ Healthy controls, Initial contact (55)│
                    └──────────────────────────────────────┘
                                      │
┌──────────────────────────────────┐  │
│ Did not meet general inclusion   │◀─│
│ criteria (12)                    │  │
│ Met exclusion criteria (4)       │  ▼
│ Withdrew or did not answer the   │ ┌──────────────────────────────────────┐
│ phone (8)                        │ │ Sleep laboratory assessment (31)     │
└──────────────────────────────────┘ └──────────────────────────────────────┘
                                      │
┌──────────────────────────────────┐  │
│ Met exclusion criteria (3)       │◀─│
│ Withdrew or did not meet (7)     │  ▼
└──────────────────────────────────┘ ┌──────────────────────────────────────┐
                                     │ Participated (21)                    │
                                     └──────────────────────────────────────┘
```
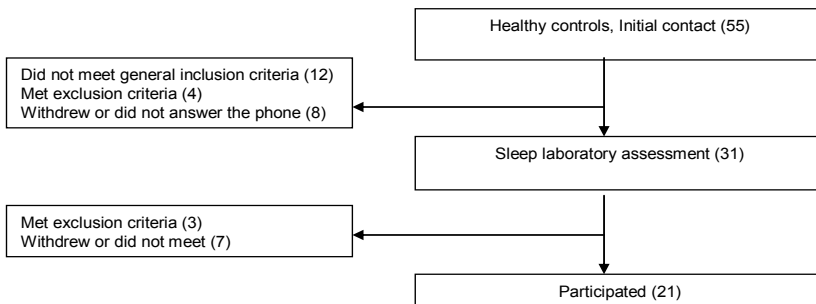
Figure 3. Participant flow in the study, control-group.

3.1.2 Instruments

Demographic information

Data were collected regarding age, gender, self-reported average school grades, school/employment status (high school/college or university students/employed) and living conditions (with/without their parents). All three papers in the thesis include some, or all, demographic information.

Dim Light Melatonin Onset

Dim light melatonin onset (DLMO) is the time in which the saliva melatonin level has raised above 4 pg/ml in saliva. We used a validated DLMO protocol (Pandi-Perumal et al. 2007). For further information and discussion of DLMO results from the study, see Saxvig and colleagues (Saxvig et al. 2013a). DLMO measures were in this thesis used for each of the participants in the qualitative study (paper 1) as background information (see Table 1, paper 1, p. 52).

Mid point of sleep

Mid point of sleep is the average middle time point between sleep onset and sleep offset. Mid point of sleep was retrieved from sleep diaries. Description of the sleep diaries is not a part of this thesis (presented in Saxvig et al., 2013a). Mid point of sleep was in this thesis used for each of the participants in the qualitative study (paper 1) as background information (see Table 1, paper 1, p. 52).

Raven Progressive Matrices

The Raven Standard Progressive Matrices (Raven 2000) are designed to measure a person's ability to form perceptual relations and to reason by analogy independent of

language and formal schooling. There are 60 items arranged in five sets with 12 items each. Each item contains a figure with a missing piece. Below the figure are either six or eight alternative pieces to complete the figure, and only one is correct. The maximum score is 60 and the test manual provides normative data for the translation of the test scores into intelligence quotients for different age groups. Intelligence quotient from the Raven test was used as a comparison measurement between the DSPD and control group in paper 2 and as background information in paper 3.

NEO-Personality Inventory-Revised

The NEO-Personality Inventory-Revised (NEO-PI-R) assesses the main personality dimensions included in the Big Five model: Neuroticism; Extroversion; Openness to experience; Conscientiousness; and Agreeableness. It measures 6 facets (each comprising 8 questions) underlying each of the five dimensions. Thus, the NEO-PI-R consists of 240 items where every item is a statement which describes a specific disposition (Costa and McCrae 1992). The respondents rate each statement on a 5-point Likert scale from "strongly disagree" to "strongly agree". We used the validated Norwegian version of the NEO-PI-R (Martinsen et al. 2005). T-scores of 20-34 are considered very low, 35-44 low, 45-55 average, 56-65 high and 66-80 very high. As the mean raw scores for males and females differ, we transformed all raw scores to gender specific t-scores (mean=50, SD=10). A description of analysis of the personality measures, compared between the DSPD group and the control group, can be found in paper 2.

Morningness-Eveningness Questionnaire

The Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne and Östberg 1976) consists of 19 items related to time of day preferences for physical and mental activities, as well as judgments of subjective alertness after rising and before bedtime. Scores range from extreme eveningness (16) to extreme morningness (86). The MEQ is the most widely used subjective tool for differentiating circadian type (Smith et al. 1989). Morningness-eveningness type for each participant was used as background information

in paper 1 and the average score on the MEQ was compared between the two groups (DSPD and controls) in paper 2.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) is a self-report instrument used to screen for non-vegetative symptoms of anxiety and depression. The anxiety and depression subscales each consist of 7 items on a 4 point Likert scale (0-3), yielding a score range from 0 to 21. The cut-off for possible depression/anxiety symptoms above what is expected in a normal population is 8 on each subscale. The anxiety and depression scores for each participant were used as background information in paper 1, as a comparison measure between the DSPD- and control group in paper 2, and as background information in paper 3.

Subjective Health Complaints

Subjective Health Complaints (SHC) (Eriksen et al. 1999) is an inventory concerning subjective somatic and psychological complaints. It consists of 29 questions regarding severity and duration, and is categorized into musculoskeletal pain, pseudoneurology, gastrointestinal problems, allergy and flu. In this study we used the total composite score of the SHC. The SHC total composite score was used as a comparative measure between the two groups (DSPD and controls) in paper 2.

Fatigue Questionnaire

The Fatigue Questionnaire (FQ) (Chalder et al. 1993) consist of 7 items related to physical fatigue and 4 items related to mental fatigue. In this study we used the score for total fatigue, which is the sum of the two subscales. We administered the validated Norwegian version of the instrument (Loge et al. 1998). The total fatigue score was used as a comparison measure between the groups (DSPD and controls) in paper 2, and for assessment of fatigue before and after treatment in paper 3.

Bergen Insomnia Scale

The Bergen Insomnia Scale (BIS) (Pallesen et al. 2008) is a self-report instrument constructed upon current formal and clinical diagnostic criteria for insomnia. It consists of 6 items, each rated on an 8-point scale, ranging from 0 to 7 days a week. The total composite score range from 0 to 42. The total composite score was used as a comparison measure between the two groups (DSPD and controls) in paper 2.

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) is a self-report questionnaire which assesses sleep quality and disturbances during the past month. It consists of 19 items and gives information about 7 components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime functioning. The global score, which ranges between 0 and 21, was used in this study. The global score was used as a comparison measure between the two groups (DSPD and controls) in paper 2.

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) (Johns 1991) is a self-administered questionnaire which provides measures of the subjects´ general (trait) level of daytime sleepiness. The subject rates the probability of falling asleep/dozing off in eight different everyday situations on a scale ranging from 0 ("no probability") to 3 ("high probability"). The maximum score is 24 and the cut-off value for excessive daytime sleepiness is 11. We used the validated Norwegian version of the ESS (Pallesen et al. 2007). The ESS score was used as a comparison measure between the two groups (DSPD and controls) in paper 2 and for assessment of general subjective daytime sleepiness before and after treatment in paper 3.

Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (KSS) (Åkerstedt and Gillberg 1990) is a scale where subjects rate their concurrent sleepiness level. The scale is verbally anchored with steps ranging from 1 ("very alert") to 9 ("very sleepy, fighting sleep, effort to stay awake"). A score of 7 or more indicates excessive sleepiness. The KSS was used for assessment of concurrent subjective sleepiness at different time points before and after treatment in paper 3.

Alpha Attenuation Test

The Alpha Attenuation Test (AAT) is a quantitative method for assessing objective sleepiness. The participants were instructed to sit comfortably in an office chair in a sound-proof chamber, to relax but to remain awake and to look at a red "X" on the wall straight ahead of them. They were asked to close their eyes and to open their eyes consecutively at two-minute intervals, three times. Thus, the total duration of the AAT was 12 minutes. Electrodes were montaged according to the AASM Manual for the Scoring of Sleep and Associated Events (Iber et al. 2007). Data were collected online with ambulatory Embla Titanum recorders and the Somnologica software package (Embla Systems Inc., USA). A single EEG derivation was used for spectral analyses (O1). Power spectrum analysis criteria were set to: power-bands alpha = 8 - 11.99 Hz, 1 second epochs, 256 point fast Fourier transform (FFT) (Welch 1967) overlapped by 0%, where the FFT`s are averaged with the selected epoch duration. We divided the average spectral alpha power of eyes closed by the average spectral alpha power of eyes open which gives a ratio of the "alpha attenuation coefficient" (AAC) (Stampi 1995). The higher the AAC is, the higher is the alertness level. The AAC measure was used for assessment of physiological (objective) sleepiness at different time points before and after treatment in paper 3.

Conners` Continuous Performance Test

The Conners` Continuous Performance Test (CPT-II) Version 5.1 for Windows®
(Conners and MHS Staff 2004) is a test of different aspects of attention. It lasts 14
minutes, and the subject is instructed to press the space bar on the computer keyboard
whenever a letter appears on the screen, except for the letter "X". The CPT-II is a test
assessing the ability to maintain focused alertness over a relatively long period of time. In
the study we included the confidence index associated with ADHD assessment, which
gives an indication of the chances out of 100 that no significant attention problem exists.
We also included an overall reaction time measure (RT for hits), number of omission
(responses that should have been given but were not) and commissions (wrong responses
given when there should be no response) as measures of accuracy and two measures of
consistency (Hit RT standard error and Variability). The confidence index measure for
each participant was used as background information in paper 1. The measures for
reaction time, accuracy and consistency were used for assessment of cognitive function
before and after treatment in paper 3.

Wechsler Adult Intelligence Scale-III

Three subtests from Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler 1997),
the Digit Symbol-, Letter-Number- and the Symbol Search Test, were used in the study
as measures of working memory/processing speed. During the Digit Symbol Test, digits
and symbols are presented as pairs and additional digits and symbols must be paired by
the subject. Letter-Number Sequencing requires that the subject order numbers and
letters that are presented in an unordered sequence. In the Symbol Search Test, the
subject must match symbols that appear in different groups. The three subtests were used
as measures of working memory/processing speed for assessment of cognitive function
before and after treatment in paper 3.

Delis-Kaplan Executive Function System

Two tests from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al.
2001), the Color Word Interference Test (CWIT) and the Verbal Fluency Test (VFT)
were used in the study as measures of executive function. From the CWIT, which is an

adaptation of the Stroop task, we included the third condition, where the subjects are presented with color words printed in incongruently colored ink (CWIT-Inhibition), and the fourth condition requiring the subjects to switch between either naming the color of the incongruently colored color-words or reading the color names when presented with a brace (CWIT-Inhibition/Switching). From the VFT, we included the condition where the subjects are asked to switch between reporting items from two different categories (VFT-Category Switching). The measures for executive function were used for assessment of cognitive function before and after treatment in paper 3.

Compliance and side effects

A form to be completed each day of the two-week treatment period was developed to measure compliance. Points were given for light exposure (one point), capsule taken (one point) and rise time (one point) at the prescribed time (+/- 1 hr). Full score was rated as 100% compliance. For the three-month follow-up, points were given for light exposure (one point) and melatonin capsule taken (one point). Full score was rated as 100% compliance. Side-effects during treatment were retrospectively recorded at the two-week assessment (participants noted any possible side-effects on a form developed for the study) and at three-month follow-up. Measures of compliance to treatment and side-effects of treatment were included in paper 3. An overview of the study protocol is presented in Table 2.

	DSPD group (N=40)		Controls (N=21)	
1st meeting	Demographic information Raven Progressive Matrices		Demographic information Raven Progressive Matrices	
2nd meeting	PSG hook-up (adaptation night)		PSG hook-up (adaptation night)	
3rd meeting	PSG hook-up (screening night)		PSG hook-up (screening night)	
	Sleep diary (1 week) Actigraph (1 week) Saliva samples (1 night)			
4th meeting	Daytime function protocol		Daytime function protocol	
	NEO-PI-R MEQ AAT CPT-II WAIS-III D-KEFS	BIS PSQI ESS SHC FQ HADS	NEO-PI-R MEQ AAT CPT-II WAIS-III D-KEFS	BIS PSQI ESS SHC FQ HADS
	2-week treatment Sleep diary (2 weeks) Actigraph (2 weeks) Saliva samples (1 night)			
5th meeting	Daytime function protocol			
	NEO-PI-R MEQ AAT CPT-II WAIS-III D-KEFS	BIS PSQI ESS SHC FQ HADS		
	3-month follow-up Sleep diary (last 2 weeks) Actigraph (last 2 weeks) Saliva samples (1 night)			
6th meeting	Daytime function protocol			
	NEO-PI-R MEQ AAT CPT-II WAIS-III D-KEFS	BIS PSQI ESS SHC FQ HADS		

Table 2. Overview of the study protocol (instruments) throughout the study. PSG=not part of this thesis. Sleep diary, actigraph and saliva samples=not part of this thesis except for the mid point of sleep from sleep diaries and DLMO reported as background information for each participant in paper 1.

3.1.3 Ethics

Informed consent was obtained after a full explanation of the study protocol (including the qualitative study (paper 1) for the DSPD-group). For participants under 18 years of age, parents were required to sign the consent form before inclusion and to give consent

verbally. All participants received a compensation fee (approximately 60 EURO for patients in the DSPD-group, approximately 25 EURO for the controls) for their time invested in the study. In cases of adverse events, guidelines for Good Clinical Practice (GCP) were followed (Switula 2000). The two research administrators/PhD-candidates conducting the trial were GCP-certified, so was the main supervisor in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway, the Norwegian Social Data Service as well as by the Norwegian Medicines Agency.

3.2 Paper 1

Participants

Informants comprised a subsample of the participants with DSPD. Recruitment was according to Patton's (1990) purposeful qualitative sampling categories partly based on convenience (six informants were selected on convenience; they were enrolled in the qualitative study in parallel with their order of enrolment in the RCT) and partly on critical case sampling (three informants were selected based on possession of good reflexivity and verbal proficiency during the first meeting) (Patton 1990). Six high school students (4 women, 2 men) and four university/college students (2 women, 2 men) aged 16-23 years (mean age=18.2, SD=2.4) were interviewed. Data from one interview (woman, university/college student, age 23) were lost because of tape failure, leaving nine transcripts for analysis.

Procedure

In-depth semi structured individual interviews were conducted from October 2008 until November 2010. The interviews lasted 25-59 minutes (mean length=39.1 minutes, SD=10.5). The interview guide was developed on the basis of knowledge from existing research on DSPD and from clinical experience. The main themes in the interview guide

were: development of the sleep pattern, beliefs about the origin of the sleep pattern, attempts to cope with the sleep pattern, consequences of the sleep pattern, thoughts about the future, and self-image. All interviews were audio taped and transcribed verbatim by the first author.

Qualitative analysis

We followed the standard four steps of systematic text condensation (Giorgi 1985; Malterud 1993, 2012). Systematic text condensation (STC) as described by Malterud (2012) is inspired by Giorgis` phenomenological analysis and has many similarities with the procedures of grounded theory (Giorgi 1985; Glaser and Strauss 1967; Malterud 1993, 2012). This method is a descriptive and explorative approach, well suited for cross-case analysis where information from different informants is being summarized. It is also suitable for novice researchers as it offers a detailed description of the process of analyses while maintaining methodological rigour (Malterud 2012).

We followed these four stages of STC: 1) total impression – from chaos to themes, 2) identifying and sorting meaning units – from themes to codes, 3) condensation – from code to meaning and finally 4) synthesizing – from condensation to descriptions and concepts. The first and second author initially developed suggestions for themes by separately reading all transcripts and discussing the emerging themes (stage one). Agreement between the coders was not sought after; we rather tried to expand possible ways of understanding the interviews. On the basis of these discussions, the first author systematically coded the units of meaning in the transcripts (stage two). Then the first author met several times with the rest of the research team to discuss the emerging codes on the basis of selected quotes from the transcribed interviews. These discussions functioned as an audit where overlapping of codes and the structure of the categories were challenged and discussed. These discussions also informed the first author in the next step, which was to abstract the meaning from the codes that seemed to cluster together thematically by developing meaningful condensates and finding authentic illustrative quotations of the different identified themes (stage three). The analysis

process was dynamic and we moved back and forth between the stages in the analysis
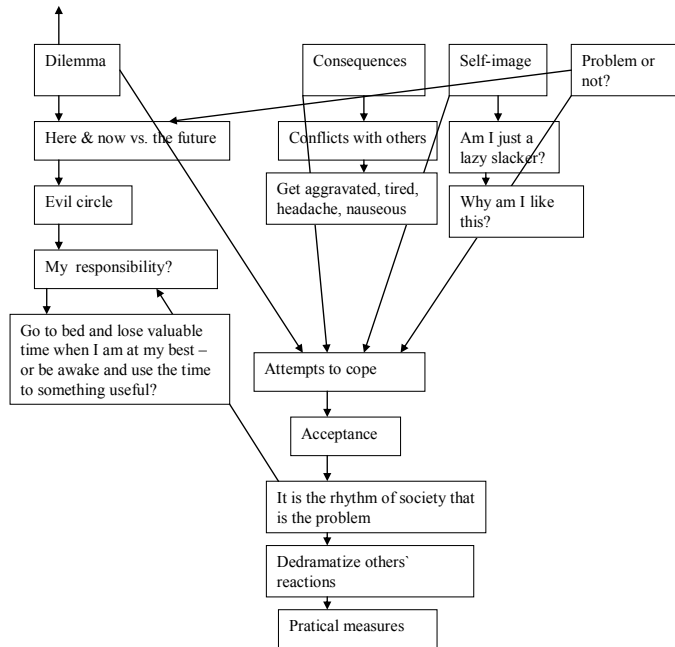several times. Figure 4 illustrates parts of the analysis process.

Figure 4. Illustration of a figure made during the analysis process.

Through further discussions in the research group, we decided on core categories
which synthesized the range of themes (stage four). Although full saturation can probably
never be achieved, by the ninth interview very few new codes were being developed, no
new main issues emerged and we therefore ended the data collection at this point. The
analysis was assisted by the NVivo 8 software.

3.3 Paper 2

Participants

The study groups consisted of all participants in the study; the 40 patients diagnosed with DSPD (30% men, 70% women) and the 21 healthy controls (28.6% men, 71.4% women) (p=1.0). Mean age was 20.7 years (±3.1) in the DSPD-group and 21.1 years (±2.2) in the control group (range 16-25 years, p=.51). In the DSPD-group, 40% were high school students, 57.5% college/university students and 2.5% employed. In the control group 19.0% were high school students and 81.0% college/university students (p=.15)

Procedure

During the first meeting for participation in the study, self-reported average school grades were obtained and the Raven Progressive Matrices test was performed as part of the screening process. During baseline assessment day for the treatment trial (4[th] meeting in table 2, page 51), the participants in both groups completed the NEO-PI-R, MEQ, BIS, PSQI, SHC, HADS and FQ.

The NEO-PI-R was chosen as the main outcome measure in paper 2 because it is developed to measure normal personality (as opposed to the MMPI-2 which is developed to measure psychopathology). First, we do not expect all patients with DSPD to have a pathological personality profile. Second, in order to compare the profile of patients with DSPD to healthy controls, we decided the NEO-PI-R would be a suitable choice. Because of common comorbidity with other disorders (Reid et al. 2012), frequently reported lack of motivation and dropping out from treatment studies, we hypothesized that patients with DSPD would have a different personality profile than a control group with similar demographic characteristics.

Statistics

IBM SPSS Statistics Version 19.0 for Windows was used for the statistical analyses. To test for differences between the two groups, one-way ANCOVA analyses were performed on all measures with high school student/college or university student/employed as covariate. When significant group differences were detected on the NEO-PI-R dimensions, we also performed one-way ANCOVA analysis on each of the underlying facets. Differences were considered significant when p-values were less than .05. Effect sizes (Cohen's d) were calculated using an online calculator (for unadjusted mean scores) (http://easycalculation.com/statistics/effect-size.php) and partial eta squared were provided in the tables for the adjusted mean scores.

3.4 Paper 3

Participants

All 40 participants from the DSPD-group participated in the treatment study.

Procedures

Participants underwent the same daytime testing protocol at three assessment points: before treatment (baseline assessment; 4[th] meeting, see table 2, page 51), after two-week treatment (two-week assessment, 5[th] meeting) and after three months of treatment/no-treatment (6[th] meeting). Prior to baseline assessment, participants had been instructed to go to bed and rise at self-chosen times for four consecutive days (Saturday, Sunday, Monday and Tuesday) in order to avoid sleep deprivation. On the assessment days, the participants were instructed to rise at 7am and to meet at the sleep laboratory at 8am. Test sessions started about every hour from 9am to about 1pm with intermediate breaks. The AAT, KSS and CPT-II were all conducted three times each assessment day, in the mentioned order, starting at approximately 9am, 11am and 1pm. All other tests were conducted once. The protocol included measures of i) subjective sleepiness and fatigue

(KSS, ESS and FQ), ii) objective sleepiness/arousal (AAT) and iii) performance on tests of cognitive function (CPT-II, WAIS-III subtests and D-KEFS subtests).

Participants were randomized into one of four treatment conditions lasting for 2 weeks in a double-blinded, placebo controlled design. The four treatment conditions were: dim light (placebo) and placebo capsules (placebo group), bright light and placebo capsules (bright light group), dim light (placebo) and melatonin capsules (melatonin group) and bright light and melatonin capsules (combination group). All groups were instructed to use dim/bright light and placebo/melatonin capsules on a gradual advancement schedule regarding rise times and treatment times. In a follow-up study, participants were re-randomized into 2 groups receiving either the treatment combination of bright light and melatonin alongside gradually advanced rise times (treatment group) or no treatment (no-treatment group) in an open label trial for approximately three months.

Lighting conditions in the testing rooms were 200 lux. Light was set to 500 lux in the laboratory where participants stayed during breaks. The laboratory had no windows. Hence, participants were not exposed to daylight while being tested. Although there are seasonal variations in daylight in Norway, these variations are likely to be spread across the sample and should consequently not influence the results. Two study administrators and one research assistant performed all tasks throughout the study.

Treatment protocol

The treatment protocol was based on the approach described by Bjorvatn and Pallesen (2009). The participants were instructed to sleep until spontaneous awakening on the first day of treatment and be exposed to the study light source for a minimum of 30 minutes immediately after awakening, with eyes directed towards the lamp. Capsules were to be taken 12 hours after light treatment was initiated. Because of the soporific effects of melatonin, capsules were not to be taken before 8pm in the evening. These instructions ensured that treatment was individualized according to how delayed each participant's circadian rhythm was. Rise time was advanced by one hour every day until the preferred

rise time was reached (each participant chose their target rise time) and then maintained until the end of the two weeks treatment period. If the participant overslept, the instructions were to be exposed to the study light lamp immediately upon awakening, to take a capsule 12 hours later and then advance by one hour every day until target rise time. No instructions were given regarding bed time. Alcohol usage was prohibited during the two-week treatment period. No instructions regarding alcohol use were given during the three-month follow-up study.

Lamplights and capsules

Lamplights were either bright white (approximately 10 000 lux at 50 cm distance) with a clear cover screen or dim (approximately 400 lux at 50 cm distance) with a red cover screen. Light lamps (ML-10 000) were manufactured by Miljølys Inc., Norway. ML-10 000 is a light box (47 x 17.5 x 29 cm) containing three fluorescent bulbs (Philips, Ecotone, P1-L, RA-index=80, light temperature 4000 K). Dim light lamps have been assumed to have minimal effect on the endogenous circadian rhythm (Lewy et al. 1980; Rosenthal et al. 1990).

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

Blinding and randomization

The two-week treatment study was double-blinded. Participants were informed that they would receive either red or white light, but not that the light intensity was different. Lamps were given to the participants packed in boxes concealing the color of the cover screen differentiated by a letter code (A and B) and the participants were instructed not to reveal the color to the study administrators at any time (blinding of light boxes was

performed by two university employees not otherwise involved in the study). Participants were further informed that the capsules contained either melatonin or maize starch. The melatonin and placebo capsules for the two-week study were packed in identical containers differentiated by a number code (1 and 2). The three-month follow-up study was not blinded.

The randomization lists were made (4 groups for the two-week intervention, 2 groups for the three-month follow-up) using the Internet based program Research Randomizer (http://www.randomizer.org/form.htm). Participants were chronologically assigned to the respective groups on inclusion.

Statistics

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

Demographic variables were compared between groups using one-way ANOVA, *t*-tests for independent samples and Pearson chi square test to investigate possible group differences at baseline. Effects of the two-week treatment period were compared between the four groups using two-way ANOVA (4 treatment groups x 2 assessment points) for repeated measures for all tests of subjective sleepiness, objective sleepiness and cognitive function. To test for differences between the groups on compliance, drop-out and side-effects, one-way ANOVA and Pearson chi square tests were performed. At three-month assessment the same variables (subjective and objective sleepiness and cognitive function) were compared between the groups (no-treatment/treatment) with respect to both the baseline assessment and to the two-week assessment using two-way ANOVA for repeated measures (2 treatment groups x 2 assessment points).

Interaction effects were further assessed using *t*-tests for paired samples. Cohen`s d (effect size) was calculated between baseline and the two-week assessment and

between baseline and the three-month assessment using an online calculator
(http://easycalculation.com/statistics/effect-size.php) with the formula: d=M1-
M2/(sqrt(SD_1^2+SD_2^2)/2).

4. Summary of results

Paper abstracts

Paper 1

Wilhelmsen-Langeland, A., Dundas, I., Saxvig, I. W., Pallesen, S., Nordhus, I. H., & Bjorvatn, B. (2012). Psychosocial Challenges Related to Delayed Sleep Phase Disorder. *The Open Sleep Journal, 5,* 51-58.

ABSTRACT

Delayed sleep phase disorder (DSPD) is a disorder where the circadian rhythm is delayed according to the conventional norms, often resulting in school- and work related difficulties as well as emotional challenges. Research on the experiences of having DSPD is lacking, and to enhance our understanding we conducted a qualitative study using in-depth semi structured interviews focusing on the challenges of having DSPD. A sample of 9 participants (16-23 years) diagnosed with DSPD was interviewed and analysis was done using systematic text condensation. A core theme in all interviews was how to cope with different challenges related to the disorder. We labelled the identified challenges: 1) To give something up; 2) To blame something or someone; and 3) To have a problem or not. Awareness of these challenges adds to our understanding of the daily struggles of those with DSPD and may improve clinicians` competence and ability to help them.

Paper 2

Wilhelmsen-Langeland, A, Saxvig, I. W., Pallesen, S., Nordhus, I. H., Vedaa, Ø., Sørensen, E., Bjorvatn, B. (2013). The Personality Profile of Young Adults with Delayed Sleep Phase Disorder. *Behavioral Sleep Medicine*, In press.

Abstract

Delayed sleep phase disorder (DSPD) is a circadian rhythm sleep disorder characterized by a substantial delay in the major sleep period, resulting in difficulties falling asleep and awakening at a socially desirable time in the morning. This study is the first to investigate the NEO-Personality Inventory-Revised profile of young adults with DSPD. We included

40 patients diagnosed with DSPD (mean age 20.7) and 21 healthy controls (mean age 21.1). Results showed that young adults with DSPD scored higher on Neuroticism, lower on Extroversion and much lower on Conscientiousness than the control group. Assessing the personality profile of young adults with DSPD before initiating treatment might provide a useful clinical guidance regarding the individual needs for follow-up during treatment.

Paper 3

Abstract

Delayed sleep phase disorder (DSPD) is a circadian rhythm sleep disorder. Patients with DSPD have problems initiating sleep if they go to bed at a conventional time and they often have problems waking at desired times. If they rise early in the morning they usually experience severe sleepiness during morning hours. In the present study we investigated short- and long term effects on measures of subjective and objective sleepiness and cognitive function of bright light and melatonin treatment alongside gradually advanced rise times in adolescents and young adults. Four treatment conditions were used in the short-term intervention (two weeks); dim light (placebo) + placebo capsule, bright light + placebo capsule, dim light (placebo) + melatonin capsule and bright light + melatonin capsule. This was followed by a long-term intervention (three months) including two conditions; no treatment and combined bright light + melatonin treatment. Effects of treatment on sleepiness and fatigue were the primary outcome measures and effects on cognitive function were secondary outcome measures. On a gradual advancement of rise time schedule, all treatment conditions (bright light, melatonin, the combination and placebo) were almost equally effective in improving subjective daytime sleepiness, fatigue and cognitive function in the two-week study. The two-week intervention showed no effect on objective sleepiness. Long-term treatment

increased some of the positive effects seen after two weeks. Combined bright light and melatonin treatment improved subjective daytime sleepiness, fatigue and cognitive function in the three-month study. The no-treatment group returned to baseline values on most variables. In conclusion, gradual advancement of rise times seems to produce positive effects on subjective sleepiness, fatigue and cognitive performance during short-term treatment of patients with DSPD. However, the benefits from gradually advanced rise times seem to wear off, suggesting that continuation of bright light and melatonin treatment is beneficial to maintain positive effects over time.

"If I could sleep until noon every day then that would be okey by me, because when I can sleep until late, I am usually rested."

(...)

"And have lots of energy and want to do things. But when I have to get up at six, seven, eight o`clock, then it is more like - ah! It is really just a hassle."

Participant in the study (quote from paper 1, p. 54)

5.   Discussion

The overall aim of this thesis was to gain new evidence-based knowledge about DSPD in order to be able to understand and help patients better. In sum, we found in paper 1 that patients diagnosed with DSPD experience psychosocial challenges regarding how to spend their time awake, regarding what/who they blame for their delayed sleep pattern and regarding whether or not their delayed sleep pattern is a problem. These three challenges are not easily overcome, especially when parents, teachers and doctors are unaware of the existence of delayed sleep phase disorder as a diagnosis, and also in the absence of knowledge about treatment. Relevant to this knowledge, we found in paper 2 that adolescents and young adults with DSPD score higher on Neuroticism, lower on Extroversion and very much lower on Conscientiousness than healthy controls. This personality profile indicates poorer psychological stability, less sociability and low sense of discipline, structure and planned behaviour. As regards to paper 3, a person with such a personality profile, would be expected to have trouble following treatment instructions and appointments. We did however find that gradually advanced rise times could produce positive effects on daytime function in the short-term (2 weeks) in these patients, but over time (3 months), chronobiotics such as bright light and melatonin were beneficial in order to maintain the positive effects of treatment on daytime function.

5.1 General discussion

5.1.1 Psychological characteristics

We found that our group of patients with DSPD had psychosocial challenges in their daily lives that are not easily overcome. These psychosocial challenges can potentially produce conflicts with others and influence identity development (Kroger 2000; Kroger et al. 2009). We also found that our group of patients with DSPD had a personality profile that might be associated with psychological instability, social weakness and low sense of striving to achieve. In addition, they had more symptoms of anxiety and

depression, fatigue and subjective health complaints than a group of controls. The challenges people with DSPD are faced with may put them in a situation leading to a vicious circle no matter what they do. There is no clear "right" way to deal with or overcome the challenges they have in their daily lives when patients are not aware of treatment options. Hence, in some ways these challenges can be represented as dilemmas where the choices made by the patients with DSPD in regards to how to handle their sleep pattern, have equally undesirable outcomes.

Our group of patients with DSPD did not score above the cut-off for what is expected in a normal population on anxiety and depression symptoms. It is important to note in this respect that participants who reported depression to a potential help-seeking degree during the telephone-interviews, were excluded (and given advice on where to get help). Hence, potential participants with DSPD and comorbid clinical depression were excluded in our study and this explains the low scores on depression in our patient group. Our results are in agreement with Takahashi and colleagues` (2000) suggestion that patients with DSPD complain of various psychosomatic symptoms. Further, Shirayama and colleagues (2003) conclude that patients with DSPD are characterized by for example increased nervousness, poor problem-solving skills that cause them to feel powerless and a tendency to egocentric emotion, inhibition and perseverance (Shirayama et al. 2003). These characteristics may lead to social withdrawal, causing a loss of social cues in synchronizing their circadian rhythm, ultimately reinforcing a vicious circle (Shirayama et al. 2003). Good interpersonal relationships and a positive sense of self-regard in adolescence and young adulthood can produce resilience towards problems later in life (Kroger 2000). It seems that our data confirm previous notions about DSPD, but also adds new information to notions already established in the literature about DSPD.

Looking more closely at our data, we found that the range of scores on the dimensions and facets on the NEO-PI-R were larger in the DSPD-group than in the control group, especially on Conscientiousness and the underlying facet scores on this dimension. The impression from the results presented in this thesis, is that the DSPD-group is heterogeneous (more than the control group), which is in accordance with other researchers' findings (Alvarez et al. 1992; Dagan 2002; Gradisar et al. 2011a). Takahashi

and colleagues (2000) also conclude that the predisposition to DSPD is heterogeneous and includes biological, genetic, social, and psychological factors.

5.1.2 Daytime function and sleepiness

A typical complaint of patients with DSPD is that they are sleepy in the mornings, when school and most jobs start, and alert in the evenings when most people start to become sleepy. The conceptualization and operationalization of sleepiness are under constant debate in the scientific literature (Horne 2010). Because of this, we included a wide range of tests measuring different modalities of sleepiness and cognitive functions, believed to be transferable to performance during a day at school or a day at work. Our findings suggest that daytime function and sleepiness improve in patients with DSPD after treatment with bright light and melatonin. The assessment took place from about 9am to about 2pm, however the questionnaires (fatigue and sleepiness) also regarded the rest of the day. In terms of individual differences in circadian rhythms, evening- and morning types have different optimal time windows for cognitive performance (Cavallera et al. 2011). Hence, the results might have been different if the assessment took place later in the day or in the evening. On the other hand, the reason why DSPD is a diagnosis in the first place is that the sleep in these patients does not match the rhythm of society, and one of the most common complaints in patients with DSPD is daytime sleepiness and an inability to be alert during morning hours.

5.1.3 Treatment

Short-term treatment

The aim of most treatment approaches for DSPD is to correct the sleep phase delay. In paper 3, effects of bright light and melatonin administered alongside gradual advancement of rise times were investigated using a randomized, double-blind, placebo controlled design. In sum, bright light, melatonin, the combination and placebo alongside

a gradual advancement schedule were almost equally effective in improving subjective daytime sleepiness, fatigue and cognitive function in the two-week study. This contradicts the findings from previous studies, where subjective sleepiness, objective sleepiness, fatigue and alertness improved significantly only after active treatment (Gradisar et al. 2011a; Kayumov et al. 2001; Rosenthal et al. 1990). The results from the two-week study in paper 3 also contradict studies suggesting an additive effect of combined bright light and melatonin treatment (Revell et al. 2006; Wirz-Justice et al. 2004). Although not statistically significant, the effect size was larger for the combination group on subjective sleepiness measured by the ESS (see Table 2 in paper 3). For the measure of fatigue, effect sizes were large after two weeks in the combination group and in the bright light group. It is possible that the two-week treatment would yield significant interaction effects between the four treatment groups if group sizes were larger (see further discussion of power analysis under the heading "Sample size and statistical power", p. 83).

Rising at gradually advanced times probably exposed the subjects to ambient light at an earlier phase than normal. In addition, the dim light of 400 lux might have had a phase-advancing effect as seen in previous studies (Dijk et al. 2012; Duffy and Wright 2005). In healthy individuals, 3 mg of melatonin in the afternoon, in combination with advanced sleep schedules, have recently been shown to produce sleepiness and fatigue in the morning (Crowley and Eastman 2013). This effect was attributed to the earlier rise times creating a circadian misalignment. It can not be ruled out that the two-week treatment in our study produced a circadian misalignment; earlier rise times did lead to less total sleep time in the participants after two weeks treatment (Saxvig et al. 2013a). It is then noteworthy that measures of subjective sleepiness and fatigue, processing speed and executive functions improved across all groups after two-weeks despite less total sleep time. This suggests that the circadian factor in sleep regulation is extremely important in terms of daytime function, and might suggest that patients with DSPD do not necessarily perform worse than controls in general, but have different optimal time windows for peak performance based on their circadian rhythm. Studies of treatment effects on daytime function in patients with DSPD are scarce in the literature and hence our results contribute with important information.

It has been assumed that patients with DSPD can not achieve advancement in sleep-phase (leading to reduction in daytime sleepiness) by behavioural means only (American Academy of Sleep Medicine 2005). However, Sharkey and colleagues (Sharkey et al. 2011) recently found that strict rise schedules could phase advance sleep in participants with delayed sleep phase. They did not assess sleepiness in that study, but our findings suggest that also participants diagnosed with DSPD can achieve positive effects on subjective daytime sleepiness by gradual advanced rise times. Cole and colleagues (2002) did find a reduction in subjective morning sleepiness in the most delayed subjects, also in the dim light group, but the effect was larger after bright than dim light.

Long-term treatment

Long-term effects of bright light and melatonin were investigated using a randomized, controlled design for three months. Subjective sleepiness measures were no different from baseline measures in the no-treatment group; hence the positive effect of two-week treatment was reversed when active treatment was terminated. The treatment group was less sleepy measured by the KSS and the ESS and reported less fatigue after three-month treatment compared to baseline. Our findings indicate that treatment of DSPD benefit from being maintained longer than two weeks to achieve improved effects on subjective sleepiness and fatigue. This is in line with suggestions by other clinical reports suggesting that maintained treatment is necessary, because otherwise the circadian rhythm tends to drift back to a delayed phase in patients with DSPD (Alvarez et al. 1992; Dagan et al. 1998b; Rosenthal et al. 1990).

Surprisingly, the no-treatment group responded slower on the reaction time measure and obtained inferior results on the consistency measures from the CPT-II after three months compared to baseline, while the treatment group had maintained their scores from baseline on these measures. Nevertheless, the no-treatment group had maintained their performance on an executive function measure, while the treatment group had improved their executive function compared to baseline on the same measure.

It is possible that all participants were influenced by the novelty of the baseline assessment, possibly influencing their alertness level (Wilkinson 1961). Thus, habituation and boredom might negatively have influenced the results on the follow-up tests. Yet, the treatment group overall maintained their improved performance from the two-week assessment to the three-month follow-up in contrast to the no-treatment group where performance declined. This is in line with the interpretation by Wilkinson (1961), that lowered reward (in our study the no-treatment group had not received treatment the past three months) increased the effect of lack of sleep or decreased arousal. Wilkinson (1961) further suggests that individual differences in these responses to lack of sleep/decreased arousal should be investigated by measuring, for example, personality. He concludes that there may be a strong link between arousal and motivation.

Although the results support the suggestions that maintained treatment is beneficial in maintaining treatment effects, we do not know how long it takes after the termination of treatment until the positive effects are eliminated. In our study, treatment effects were almost eliminated (back to baseline levels) after three months in the no-treatment group. How long it takes for treatment effects to wear off, is still unanswered. Also, the time-frame to reach optimal treatment effects on measures of subjective sleepiness, fatigue and cognitive function is yet to be discovered.

There is little knowledge of teratogenity, interaction effects and long-term effects of melatonin (Arendt 1997). More controlled studies are warranted in order to establish recommendable treatment approaches (Bjorvatn and Pallesen 2009; Gradisar et al. 2011a; Mundey et al. 2005).

Compliance

In the two-week study, compliance was high across all groups (see paper 3, Results section) and the lack of differentiating results between the active treatment groups and placebo cannot be attributed to differences in compliance. It seems that even though the group of patients with DSPD seemed to have a personality profile suggesting difficulties in maintaining treatment instructions, they were still able to do so over a short-term

period. Regardless of personality profile, motivation might have played a part in this; however we did not assess motivation, which is a limitation of our study. Motivational interviewing (Hettema et al. 2005) before initiating treatment might have revealed and increased the participants` level of motivation for treatment and might be a suggestion to include in future research on the treatment of DSPD.

For the three-month treatment group, compliance was, as expected, lower (see paper 3, results section) but still satisfactory from a clinical viewpoint. Thirteen participants (65%) were rated as compliant to treatment (≥50% compliance) and 7 as not compliant (35%). Of the 13 who were rated as compliant, average compliance was 78% (range 57-100). Of the seven who were rated as not compliant, average compliance was 13% (range 0-39). If compliance was higher in the three-month treatment group, the results might have been different (as indicated by the measures in table 3). The differences between the two groups in table 3 are not statistically significant; however the size of the treatment group may have been too small to detect differences across subgroups. Our aim was to assess the effectiveness of a treatment modality that is readily available in for example a primary care setting with limited time per patient. Some patients with DSPD might however need closer follow-up in order to adhere to treatment. Table 3 shows the scores at three-month follow-up for measures of objective and subjective sleepiness and fatigue for the treatment group divided in subgroups of "compliant" and "not compliant".

Instrument	Compliant n=13	Not compliant n=7
KSS	5.3 ± 1.7	6.1 ± 1.7
ESS	4.9 ± 3.0	6.3 ± 3.9
FQ	9.8 ± 4.3	10.3 ± 2.4
AAC	5.2 ± 4.7	5.6 ± 4.5

Table 3. Compliant=compliant (≥50% compliance) to treatment in the three-month treatment condition. Not compliant=not compliant (<50% compliance) to treatment in the three-month treatment condition. KSS=Karolinska Sleepiness Scale, ESS=Epworth Sleepiness Scale, FQ=Fatigue Questionnaire, AAC=Alpha Attenuation Coefficient.

Drop-out

Forty participants were allocated to treatment conditions, and 35 completed. Two participants dropped out of the two-week study and three from the three-month follow-up study (see figure 2, p. 43 for explanation). This means we had a 12.5% drop-out rate in our study. Table 4 shows an overview of drop-out rates from randomized studies for the treatment of DSPD. In sum, drop-out rates from previously controlled treatment studies with melatonin for DSPD range from 0% to 40% and drop-out rates from treatment studies with bright light vary from 0% to 39%. It seems that the drop-out rate in our study is comparable to other treatment studies on DSPD and is more in the lower range than in the higher range. In comparison to another patient group, a meta-analysis on antidepressant response shows that drop-out rate in placebo-controlled studies was 37.7% (SD=13.1), covering 18 such studies (Rutherford et al. 2012).

Publication (authors, year)	Treatment condition	N	Drop-out rate
Gradisar and colleagues, 2011	CBT + bright light	49	18%
Rahman and colleagues, 2010	Melatonin	20	0%
Lack and colleagues, 2007	Blue LED masks	18	0%
Mundey and colleagues, 2005	Melatonin	22	40%
Cole and colleagues, 2002	Bright light masks	59	8.5%
Kayumov and colleagues, 2001	Melatonin	22	9%
Nagtegaal and colleagues, 1998	Melatonin	30	16.6%
Dahlitz and colleagues, 1991	Melatonin	8	0%
Rosenthal and colleagues, 1990	Bright light	33	39%

Table 4. CBT=Cognitive behavioral therapy.

Side-effects

Reported side-effects were headache, nausea, discomfort in eyes and skin irritation (see paper 3, results section for details). Side-effects were not serious or long-lasting. In terms of long-term treatment with bright light and melatonin, which is virtually non-existent in the research literature, it seems that this treatment is safe. However, we did not evaluate long-term effects of melatonin in other ways than recording self-reported side-effects. Thus, we can not rule out other negative effects of melatonin.

5.2 Methodological discussion

5.2.1 Methodological discussion of the qualitative study

The researchers` standpoint

When conducting a qualitative study, it is important that the researcher is reflexive about her/his own standpoint. Reflexivity can be said to mean "bend back upon oneself" (Finlay and Gough 2003). Especially within the qualitative research tradition, researchers can transform their subjectivity from being a problem to being an opportunity (Finlay and Gough 2003). Some reflexivity issues relevant for the qualitative study in this thesis, are presented and discussed in the following.

Positioning the self

Qualitative researchers today accept that the researcher is a central figure who actively constructs the collection, the selection and the interpretation of data actively (Finlay and Gough 2003). The results are therefore a product of the researcher, the participants and the relationship between them. Malterud (2012) points out the necessity of being transparent about your own understanding and preconceptions before starting a qualitative research project. In order to gain knowledge from your research and not just confirm your preconceptions, being reflexive is a must (Malterud 2012). The question is not *whether* the researcher influences the research process, but *how* (Malterud 2003). In the following, some reflexivity issues defined by Malterud (2003) are presented. The researcher and first author will be referred to in the first person.

What was my experience with the subject that was studied? I initially had little experience with DSPD but my experience grew as the number of included participants in the study increased. My initial lack of experience with DSPD might have influenced the way the interviews were conducted, in both positive and negative ways. I did not have a background that would allow me to immediately understand what the participants were talking about. On the positive side, I could not jump to conclusions. In short, I did not

have a preconceived expectation that the participants should respond in ways "typical" of participants with DSPD.

How is my position different from someone with a different experience? I am a PhD-candidate, a psychologist and a woman. My previous experience with qualitative methods is limited to my thesis in the professional school of psychology, which I wrote in 2006. I also have some experience working with adolescents. In addition, I was not an experienced sleep researcher when I started my PhD-work. Based on this, my starting point can be considered as being quite open. However, adopting the view of my supervisors might have been a possible pitfall to being inexperienced. I attempted to counter this pitfall by discussing the interviews with other colleagues with both medical and psychological backgrounds. As my knowledge of the research in the field and of the clinical aspects of DSPD continued to increase, I noticed that I was increasingly able to develop my own opinions of what was being communicated to me in the interviews.

What were my expectations about what I would find? When the interview guide was made, I asked those of my supervisors who had clinical experience working with this patient group, to write down the answers they expected to get from the questions in the guide. The purpose of this was to be transparent about what they and I expected to find. We expected to find that the participants thought it was tiring not to be able to fall asleep; that is was a problem for them, for their parents and their teachers; that they became tired and unfocused from loss of sleep; that it had consequences for their schooling and education and that it could become a problem later when they look for a job; and finally that participants would have tried to advance their delayed sleep phase by going to bed earlier and getting up earlier, with limited success.

Why was I expecting to find exactly this? We expected to find the abovementioned issues partly because it is mentioned in the research literature, and partly because our research group had experience with patients that indicated these issues to be problematic.

What is my professional perspective and viewpoint in seeking knowledge about this subject? I was interested in how this qualitative study could improve the (clinical) understanding of the people suffering from DSPD. As a psychologist I was interested in how the illness can be treated, but primarily I saw it as crucial to be able to understand

the everyday life of the people who have DSPD. Also, since I have type I diabetes, I have grown an interest for the patient-perspective in psychology, psychiatry and medicine. My engagement in the diabetes field the past years originates from my experience of being a patient myself, having an illness, how that influences my every day life and how health care professionals handle the helper-patient relation.

What was my theoretical frame of reference before the project started – what models, concepts and research traditions directed my way of thinking about this? My previous experience with similar work is interviewing children (age 8-12) about their experience of growing up with parents who have type I diabetes. My theoretical frame was then developmental psychopathology. This project (paper 1) is a descriptive and exploratory project where I tried to stay as open to a theoretical angle as possible. My background as a clinical psychologist interested in cognitive behavioural therapy may have influenced my focus in the interviews towards coping and health.

What would be different if I had read other literature or belonged to a different theoretical tradition as the project started? One might speculate that if I had not been a clinical psychologist, the interviews might have been more directed towards medical solutions to the participants' problems. Thus, I might have received more information relevant to a medical model, such as what remedies and advice they had tried to solve their problems. Instead, my focus was upon what challenges the adolescents and young adults faced and how they attempted to cope with them. In this type of research, it is important to wonder, be curious and try to explore as much as possible. My exploration was directed towards non-medical solutions to the participants` problems.

Who was I to them and how did I influence the informants? The interviews took place after the first meeting. The fact that I had diagnosed them with DSPD might have had them think about me as adhering to a medical model. They were however informed that I was a psychologist and a researcher. Knowing I was a psychologist, might have made them more willing to talk to me about their feelings. Knowing I was a researcher might have made them try to think of all aspects that might be useful for me to know.

One main point of being transparent about reflexivity issues, is not to be aware of *whether*, but *how* these issues might have influenced the research (Malterud 2012).

Through the interviews and the analysis process, I did try to bracket my preconceptions in order to direct my critical attention towards the experiences of the participants. As opposed to seek to find the "truth" about patients with DSPD, the study in paper 1 reports the life world of some patients with DSPD. Experiences from the life world of a limited number of participants are valid knowledge according to Malterud (2012). The results would probably be different if another researcher did a similar study; hence qualitative research does not aim at being replicable. I believe that paper 1 adds new knowledge and new ideas to the field of research on DSPD, most importantly that these adolescents and young adults face important challenges that they cope with in the individual ways they described in the paper.

5.2.2 Study designs

Paper 1

Paper 1 was a qualitative study with in-depth individual interviews. Qualitative research is well-suited for developing new descriptions and ideas, which was our aim for the study in paper 1. To our knowledge, this was the first qualitative study ever exploring the experiences of patients with DSPD. The informants described their experiences of having DSPD as something we framed as three main specific challenges:"To give something up", "To blame something or someone" and "To have a problem or not". As we developed new ideas that we had not thought of before, we argue that the qualitative approach served its purpose. It would be difficult, if not impossible, to get the same results by a different research design, especially a quantitative design would not be suitable for our aim.

Paper 2

We compared the results of patients with DSPD to those of a control group from the same culture, environment and age range, instead of relying exclusively on normative

scores, often based on samples from other cultures. Descriptive, observational studies give no information regarding the direction of cause and effect. To our knowledge, the study reported from in paper 2 is the first study investigating the Big Five personality profile of patients with DSPD. The study adds new and important information to the research on young adults with DSPD. However, future studies of longitudinal designs are warranted to investigate causal relationships between DSPD and personality constructs.

Paper 3

To our knowledge, this is the first study that systematically investigates the effect on daytime function of bright light and melatonin in the treatment of DSPD. Previous studies of effects of bright light have included behavioral instructions of advanced rise times, but no studies on the effect of melatonin have included a gradual advancement of rise times in their treatment protocol. This study is the first to assess both short- and long-term effects of treatment using a controlled design combining bright light, melatonin and gradual advanced rise times. It is also the first controlled study investigating the effect of bright light and melatonin on objective and subjective sleepiness and cognitive function in adolescents and young adults diagnosed with DSPD.

The two-week study was randomized, placebo-controlled and double-blinded. This design should reduce potential bias in participant expectations to treatment and ensure reliable assessment of treatment effects. The three-month follow-up study was not blinded or placebo-controlled and differences in results are at risk of being explained in terms of expectation bias. We did not record the participants` expectations to treatment in the two-week or the three-month study, which represent a limitation.

5.2.3 Procedures

The screening process, recruitment, inclusion and exclusion criteria

Our study sample in the DSPD-group was biased to help-seeking individuals as they were recruited to participate in a treatment study. The control-group might have had less to gain from participation in the study as they were simply contributing to research, possibly being different from people who would not volunteer to contribute to research.

The participants in the study were thoroughly screened for other pathologies. Hence, anxiety, depression or attention disorders can thus be ruled out as probable confounders to our results. However, the results may, on the other hand, not be directly transferable to patients with DSPD who suffer from comorbid disorders. Also, our participants scored somewhat above average range on self-reported school grades and intelligence, which may represent a bias towards relatively well-functioning patients with DSPD compared to patients that we commonly meet in sleep clinics, e.g. those who have dropped out of school or who are unemployed because of their sleep disorder. Finally, one inclusion criterion for the DSPD-group was that the participant should fall asleep after 2am three or more times a week. By choosing this criterion for our study, we might have excluded mild cases of DSPD, as a person who falls asleep at 1am most nights (and might be diagnosed with DSPD in a clinical setting), would be excluded. Hence, results might not be generalized to the mildest cases of DSPD. The rather strict inclusion criteria in our study most likely also contributed to difficulties recruiting participants to the study. On the other hand, it was important to include participants who were otherwise healthy and able to follow the full study protocol.

Randomization and blinding procedures

The participants in the DSPD-group were chronologically allocated to the different treatment conditions on enrolment; hence there was no allocation bias. We adhered to the allocation lists, which were ensured by the monitoring procedures in the study. As regards to the blinding procedures, it is possible that the participants receiving dim (red)

light (placebo) might have realized that their light was not particularly bright. Hence, the blinding might not have been blind to all participants. There was also a potential risk of the colour of the lamp screen being revealed to the study administrators. However, no such revelations occurred and the study administrators remained blinded to the treatment groups in the two-week study until the code was broken after scoring and punching of data were completed.

Treatment protocol

The dim light lamps used in the two-week treatment were used as placebo because they according to previous studies should have limited chronobiotic effect (Lewy et al. 1980; Rosenthal et al. 1990). However, more recent research has indicated that dim light at optimal times may have phase-setting effects (Boivin et al. 1994; Dijk et al. 2012; Duffy and Wright 2005). We cannot rule out that also the groups who received dim red light in the two-week study benefitted from an advancement of their circadian rhythm. It is possible that parts of the positive effects after the two-week assessment were due to the effect of light in all groups. The behavioural instructions to gradually advance rise times in itself, probably led to earlier exposure to ambient light, which possibly had a positive effect. The no-treatment group in the three-month follow-up study had become familiar with the positive effects of a gradual advancement of rise times, but they were neither encouraged nor discouraged to continue this behavior. This fact, however, may differentiate them from a wait-list comparison group.

We did not evaluate the circadian rhythm of patients with continuous measures of core body temperature or melatonin levels. Hence, we can not rule out the possibility that some participants were exposed to the study light lamps before CTmin, which would delay the circadian rhythm. Also, if participants slept long after CTmin, the optimal phase-advancing time window might have been passed. There is lower risk of melatonin being taken at a phase-delaying time; however it has been shown that different doses of melatonin have different optimal time windows for phase-advancing effects (Burgess et al. 2010). In sum, we can not rule out the possibility that treatment at more optimal

circadian times might have produced larger treatment effects. Also, the results from paper 3 may not be directly transferable to treatment with lower intensity lux and other doses of melatonin taken at other times of the day. However, the behavioural indication of treatment start time used in this study (instructing the participants to sleep until spontaneous awakening on the first day of treatment and then be exposed to light), should ensure that the participants were exposed to light after CTmin. If the participants woke up early, they were instructed to sleep until they felt rested. Hence, instructions were given to ensure that light was administered at the phase-advancing part of the circadian rhythm.

5.2.4 Validity of instruments

Tests and questionnaires (subjective self-evaluations)

The tests and questionnaires in the study (Raven Progressive Matrices, NEO-PI-R, MEQ, HADS, SHC, FQ, ESS, KSS, PSQI, BIS) are commonly used and well-validated (Buysse et al. 1989; Chalder et al. 1993; Egger et al. 2003; Eriksen et al. 1999; Horne and Östberg 1976; Johns 1991; Loge et al. 1998; Martinsen et al. 2005; Pallesen et al. 2008; Pallesen et al. 2007; Raven 2000; Zigmond and Snaith 1983; Åkerstedt and Gillberg 1990). However, these tests and questionnaires are self-report instruments and wrongful responses cannot be ruled out. On the other hand, all participants were screened with the SCID-I and hence a clinical interview and evaluation was performed in addition to the self-evaluations.

The NEO-PI-R is validated from the age of 17. Five participants in the DSPD-group and one participant in the control-group had not turned 17 when the NEO-PI-R was administered. This represents a methodological limitation; however it is not likely to have influenced the results.

Tests of objective sleepiness and cognitive function

To our knowledge, this is the second study to assess objective sleepiness in patients with DSPD and the first to assess objective sleepiness in patients with DSPD using the AAT. Although several studies have validated the AAT as a test to measure objective sleepiness and that the test correlates with tests of subjective sleepiness (Alloway et al. 1997; Kaida et al. 2006; Stampi 1995), the test has not been validated in this patient group. In our study, the AAT results did not follow the same pattern as the KSS or the ESS. Stampi (1995) found that the AAT may not be a sensitive measure in high alpha producers. The mean AAC in our group of patients with DSPD was 4.7 ± 4.2 and seems to be higher than the mean AAC from other studies. In a study comparing a group of patients with narcolepsy to normal sleepers, mean AAC was 1.4 ± 0.7 for the patients with narcolepsy and 2.5 ± 1.4 for the normal sleepers (Alloway et al. 1997). In the study by Stampi and colleagues (1995), their healthy participants had an AAC mean of 3.9 ± 0.8 on the first day and 2.1 ± 0.5 after 40 hours of sleep deprivation. The AAC means may not be transferable from one group of participants to another or from one study to another (due to different technical equipment and/or differences in frequency band criteria etc.). Another explanation might be that the alpha power density in DSPD patients is different from healthy persons without a circadian rhythm sleep disorder. The AAT may be regarded mainly as a measure of physiological arousal while the MSLT is a measure of sleep propensity; hence these two objective measures of physiological sleepiness seem to reflect different sleepiness modalities.

The AAT has proven to provide a quick and practical objective assessment of excessive daytime sleepiness in patients with narcolepsy (Alloway et al. 1997). The AAT is objective, minimally intrusive and more easily implemented than the MSLT and the Maintainance of Wakefulness Test (MWT) (Stampi 1995). It is not dependent on inter-scorer variability as the MSLT, as the AAT can be scored by someone who is not a trained polysomnographer. In our study, it was important to include a test of objective sleepiness that did not alter the participants` state. If we were to include the MSLT in our daytime function protocol, naps would most likely occur and confound the measures on the tests of cognitive function (Lovato and Lack 2010).

The tests used to assess cognitive function are not developed as tests of sleepiness. However, while assessing the effect of sleepiness, sleep deprivation, sleep debt and other sleep disturbances on daytime function, it has become increasingly more common to include cognitive tests. How sleepiness and sleep deprivation affect such measures is still debated and under investigation. The tests we included in this study (CPT-II, WAIS-III and D-KEFS) are widely used and well-validated standardized cognitive tests to measure aspects of attention and executive function (Conners and MHS Staff 2004; Delis et al. 2001; Wechsler 1997). We can not rule out that the improvements seen across groups on cognitive functions after two weeks might be attributed to a practice effect (Horne 2010; Van Dongen et al. 2003). On the other hand, the two-week intervention also produced positive effects on subjective sleepiness. Hence, we attribute the improvements after two weeks across all groups to positive treatment effects, not solely placebo effects or practice effects.

The most surprising finding in the three-month study was that the measures of AAC did not follow the pattern of measures of subjective sleepiness but rather followed the measures of reaction time and consistency. The novelty of the situation the first day of testing, has previously indicated increased alertness (Wilkinson 1961). Furthermore, "testing fatigue" has been suggested in previous studies, which is different from sleepiness due to sleep debt (Horne 2010). This phenomenon was possibly found in an 8-hour time in bed condition in the widely cited study of the cumulating cost of additional wakefulness by Van Dongen and colleagues (2003). While Van Dongen and colleagues (2003) attribute the decrements in reaction time measured by the PVT mainly to a small sleep debt, Horne (2010) argues that what they might have revealed was a "PVT fatigue". The CPT-II in our study is similar to the PVT, it is boring and unstimulating. It is of interest that we found that the no-treatment group showed such a "CPT-II and AAT fatigue", while the treatment group did not. It seems that there are many factors at play here. The motivation of the treatment group to "show the positive effects of treatment" might play a part, or the affective state of the participants (Franzen et al. 2008). The participants in the no-treatment group might have had little motivation to do a good job at the three-month follow-up as they had not really gained anything from participating in the study the past three months. But also, an underlying physiological sleep propensity in

the no-treatment group, might have been unmasked or uncovered by the dullness of performing such tasks for the third time (three times each assessment day). In line with this, an underlying physiological sleep propensity in all groups, might have been masked or overridden by the novelty, and possibly excitement of the first assessment day (Wilkinson 1961). In a clinical perspective, one might argue that dull, unstimulating situations are more transferable to everyday situations (tasks at school and work) than novel test-situations in a laboratory (Wilkinson 1961).

5.2.5 Analyses

Paper 1

The coding in the analysis process was done by one researcher, hence inter-rater coding was not performed. This might be a limitation as the researcher was a novice in qualitative research and could benefit from coding parallel to an expert. However, we tried to amend for this by frequent discussions in the research group regarding all four stages in the analysis process. This process functioned as an audit where the novice researcher's presentation of material such as codes and quotes to support themes, as well as descriptions of categories and condensates, were challenged by the research group.

Paper 2 and 3

Sample size and statistical power

The sample size in the comparative study (paper 2) was rather small, thus the statistical power needed to detect minor group differences might have been limited. Initial power analyses were performed and to be able to detect effect sizes of 0.5, setting alpha to .05 (two-tailed) and power to .80, it was implied that 60 participants were needed in each group (control- and DSPD-group). On the other hand, the results in paper 2 imply that the group differences detected in the present study most likely is of a clinical meaningful

magnitude, a suggestion corroborated by the large effect sizes concerning many of the group comparisons.

The sample size in the treatment study (paper 3) was quite large but the small group sizes in the four-armed two-week trial may still represent a limitation. Initial power analysis was performed. Effect sizes of about 1.1 were expected based upon results from previous studies within this field. Based upon a significance level of .05 (two-tailed) and power set to .80, 15 subjects were requested for each condition. However, recruitment to the study was more time-consuming than expected and because of time- and funding limitations; we had to terminate inclusion before the requested number of participants were enrolled. The small group sizes might account for the fact that no differences between the groups were observed in the two-week study.

Group differences in paper 2 and 3 were reported in terms of statistical significance as well as effect size calculations (Cohen`s d). Effect sizes provide information about the size of the differences observed between the groups or assessment points and are less inferential to type I- and type II errors occurring. Hence, effect sizes yield improved clinical interpretation of the findings.

Missing values and intention to treat

In the treatment study, missing values and values for participants who withdrew (drop-outs) from the study were moved forward (replaced manually) from baseline. In the two-week study, two of the 40 participants withdrew (one from the melatonin group and one from the bright light group), while three of the 38 participants re-randomized to the three-month follow-up withdrew (one from the treatment group, two from the no-treatment group) (see Figure 2).

In paper 2 and 3 there were three missing values for average self-reported school-grades in the DSPD-group as these participants had not been given any grades recently. In paper 3, the baseline assessment of the AAC-value for one participant (melatonin group in the two-week study and treatment group in the follow-up study) could not be

scored because of technical failure. CPT-II values from the 9 am assessment were missing for one participant. There were two missing values from the D-KEFS subtest CWIT because two participants were colour-blind (one in the placebo and one in the bright light group; one in the treatment group and one in the no-treatment group). Analyses where values from drop outs and missing values were excluded yielded similar results as the intention to treat analysis (data not presented in the thesis).

5.2.6 Ethics

Informed consent was obtained after a full explanation of the study protocol; however some participants were under the age of 18 and required parental consent. Although not required, all participants under 18 also signed the consent form. Some participants participated in the whole study (approximately a 4 to 5-month period) without receiving any active treatment. Because treatment guidelines for the treatment of DSPD do not exist, this was not considered ethically questionable. This was also thoroughly explained at the first meeting. By the end of the study, we did however recommend interested participants treatment options if they asked. On the other hand, the results show that all participants achieved some positive effect of the two-week intervention, also the placebo group. All participants regardless of condition in the two-week study were instructed to gradually advance rise times and had become familiar with the positive effects of these instructions.

5.3 Clinical significance and future implications

We know more about DSPD patients based on the results in this thesis and the overall aim has been reached. The voices of patients with DSPD have been heard and the significance and implications of study 1 are that having DSPD may lead to psychosocial challenges. Because of the lack of knowledge in the population and in primary health care, informing schools, parents and general practitioners about DSPD would be

beneficial for those suffering from it. More awareness about the disorder could reduce the inter-relational problems many with DSPD face and the negative evaluation of them (by others and by themselves) as simply being lazy slackers who do not go to bed and can not get up in the morning. It is estimated that 326 069 adolescents between 15 and 19 years and 339 047 young adults between 20 and 24 years live in Norway as of January 1st 2013 (Statistics Norway). Based on the prevalence rate of debilitating delayed sleep phase in Norwegian adolescents assessed by our research group (Saxvig et al. 2012), about 33 000 adolescents and young adults between 15 and 24 years might be affected. Hence, the first future implication is to raise awareness about the disorder. This can be done by knowledgeable researchers being active in the media and promoting the importance of this knowledge at seminars and conferences for educators, teachers, parents and health care personnel in primary care settings.

In paper 2 we found that patients with DSPD score low on Conscientiousness, which in itself might be an obstacle for future education and work relationships. The personality profile might be an explanation for why some patients with DSPD drop out of studies and have trouble persisting to treatment. However, a future implication is to assess whether they develop this personality characteristic because they have DSPD or if they develop DSPD more easily because of a lackadaisical personality. Considering the vulnerability of adolescence and young adulthood and the importance of a positive identity development, it seems that knowing how DSPD might influence the young persons` development is an important issue. Clinically, early treatment might be crucial for later school performance and for a positive identity development. We can not say based on the results from paper 2 whether the low scores on the Conscientiousness dimension predispose a person to develop DSPD, but it is an interesting research question. It would also be interesting to study if Conscientiousness scores would increase after successful treatment for DSPD and if low scores on Conscientiousness can predict treatment outcome. To study this, one would need to assess NEO-PI-R scores before and after treatment in a large sample of patients with DSPD. However, mean-level change in personality traits across the life course seem to increase in measures of Conscientiousness especially in young adulthood (age 20 to 40) (Roberts et al. 2006). Hence, to study if treatment could cause an increase on mean scores on Conscientiousness in a group of

patients with DSPD, one would also need a DSPD control group that received no treatment over many years, which would be ethically questionable. The cause and effect of the presented personality profile in patients with DSPD remains to be solved in the future and more studies on personality and DSPD are warranted.

Currently, no treatment guidelines exist for DSPD; however specialist sleep clinics normally treat patients with DSPD with bright light and/or melatonin. The results from the treatment study in paper 3 have clinical significance in that adhering to strict rise time schedules for the short-term treatment for DSPD seem beneficial in producing improvements on subjective sleepiness and some cognitive functions. These instructions can be given by anyone with knowledge about diagnostics, circadian rhythms and sleep regulation. No equipment is needed and instructions can easily be implemented in the treatment for this sleep disorder. However, in order to maintain treatment effects and optimize the improvement on subjective daytime sleepiness and cognitive function, chronobiotics seem to be necessary. This treatment protocol requires a bright light lamp and/or fast release melatonin. In this study we did not resolve the question whether bright light is more potent than melatonin in improving effects on daytime sleepiness in patients with DSPD and future randomized, controlled studies are warranted to resolve this issue. The effects of treatment on circadian rhythm (for example DLMO) and sleep (for example sleep diary and actigraphy) need to be explored further and were included in our study. These data have recently been published (Saxvig et al. 2013a) and are discussed in the PhD-thesis by my colleague on this project, Ingvild West Saxvig. Future research is also warranted to resolve the issue of whether treatment at intermittent days could maintain treatment effects. Also, more research is still needed to resolve the issues of the dose and timing of melatonin treatment, the length and timing of exposure to light and different wavelengths of light in the treatment of patients with DSPD.

"I do sort of make good use of my day because I stay up longer, but then everything else is closed and shut and sleeping, you know?"

Participant in the study (quote from paper 1, page 54)

5.4 Conclusion

DSPD is a disorder that affects the patients on many levels (i.e. psychological, social, relational, developmental, physiological and cognitive). By raising awareness about the disorder and its characteristics, many young people with DSPD might be led on a more positive path. The simple knowledge that rise times are the most important in order to entrain the delayed circadian rhythm, not bed times as commonly assumed by the lay man, could have implications in many families and classrooms. This knowledge can possibly also reduce inter-relational problems. Gradual advancement of rise times seemed to be beneficial in producing positive effects on subjective sleepiness, fatigue and cognitive performance in short-term treatment of DSPD. However, the benefits from gradually advancement of rise times seemed to wear off, suggesting that continuation of bright light and/or melatonin treatment is needed to maintain positive effects of treatment over time.

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