Chapter 6
Delayed Sleep-Wake Phase Disorder

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Introduction

Delayed sleep-wake phase disorder (DSWPD) is the most common circadian rhythm sleep-wake disorder (CRSWD) observed among adolescents and is encountered less frequently among older demographics [1, 2]. Roenneberg et al. [3] identified a prevalence inflection point of *delayed circadian preference* which reaches its maximum around 20 years of age, followed by a reversion toward an advanced circadian preference.

Individuals with DSWPD exhibit an extreme "night owl" preference that results in an inability to initiate sleep and to arise at conventional "early bird" times [4]. Resultant chronic sleep deprivation and sleep inertia (an inability to achieve full alertness upon arising in the morning) result in impaired daytime function [5]. Difficulties conforming to traditional school, social, and employment schedules may cause considerable distress for patients and those within their orbits. Mood disorders, maladaptive sleep-related behaviors, and other comorbidities complicate the individuals' attempts to self-correct and, by relation, clinicians' attempts to manage symptomatology [6–9]. The precise etiology of DSWPD is unclear, but it appears to relate to both endogenous and exogenous factors. Evidence-based treatment options are limited, but one can employ rational therapeutics utilizing a combination of scientific knowledge and accumulated clinical experience.

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Clinical Features

The International Classification of Sleep Disorders, Third Edition (ICSD-3) [4], provides diagnostic criteria for DSWPD (Table 6.1) and describes typical associated symptoms. The manual also refers to useful complementary assessment tools, including chronotype questionnaires [10] and physiologic measurements of circadian timing, such as the dim light melatonin onset (DLMO) [11]. Use of the latter as a diagnostic tool has demonstrated controversial findings.

Murray et al. [12] reported on DSWPD subjects recruited from the communities of Melbourne, Sidney, and Adelaide, Australia. The authors looked at the timing of DLMO as related to the participant's desired or required bedtime (DBT). Subjects maintained their usual sleep-wake patterns (documented with sleep diaries and wrist actigraphy) for at least 7 days prior to coming into the laboratory. If DLMO occurred at least 30 minutes prior to the participant's DBT, the subjects' sleep difficulties were deemed non-circadian in nature. Forty-three percent of DSWPD participants ($n = 79$, age 28.7 ± 9.8 years) exhibited this finding, with a mean DLMO 1.48 ± 0.78 hours before their work or school night DBT (10:49 PM ± 49 minutes), which was 3.20 ± 1.06 hours prior to their habitual sleep time (11:52 PM ± 1:16 hours). While this would appear to delineate physiologic versus behavioral DSWPD, the significance of this distinction (e.g., from a treatment perspective) is indeterminate at this juncture.

Sonheim et al. [13] highlighted DSWPD symptoms and impairments in an objective fashion, including the disabling complaint of sleep inertia that commonly occurs subsequent to early rising related to early school or work start times. Their study included 9 rigorously diagnosed Norwegian patients aged 22.5 ± 2.2 years (four males) and a matched healthy control group. Not unexpectedly with a polysomnogram (PSG) start time of 12:00 AM, sleep latency was greater in patients than in controls [41 ± 37 vs. 7 ± 7 minutes, respectively ($p = 0.003$)] and total sleep time was reduced [333 ± 49 minutes vs. 379 ± 22 minutes, respectively ($p = 0.01$)].

Table 6.1 International Classification of Sleep Disorders, Third Edition, diagnostic criteria for delayed sleep-wake phase disorder

A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of inability to fall asleep and difficulty awakening at a desired or required clock time.
B. The symptoms are present for at least 3 months
C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24-hour sleep-wake pattern
D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both workdays/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Source: American Academy of Sleep Medicine (2014)

At 7:00 AM an alarm clock was activated that started at 72 decibels (dB) for a duration of 4.4 seconds, with increases in 2 dB increments at 5-second intervals until the subject was awake or a maximum of 104 dB was reached. If this maximal stimulus failed to produce an arousal from sleep, the subjects were awakened manually. Three (33%) of the DSWPD patients (but none of the controls) failed to awaken to the alarm and remained in rapid-eye-movement (REM) sleep. The awakening thresholds of the other six patients were not significantly different than those of controls. The subgroup that did not arouse to the alarm had less REM sleep percentage than their arousable counterparts (14 ± 5% vs. 19 ± 2%, respectively $p = 0.04$) and more stage N1sleep (35 ± 9 minutes vs. 17 ± 12 minutes, respectively $p = 0.04$).

Immediately upon awakening all participants were given a continuous performance test [14], each serving as his/her own control, with comparison of scores from their baseline evening assessment. Healthy controls showed a statistically insignificant improvement of 3.4% in their morning response times compared to the previous evening (347.8 ± 59.6 milliseconds [ms] vs. 335.9 ± 56.9 ms). In comparison, the nine DSWPD patients showed an 8.6% statistically significant worsening in response times (300.6 ± 25.9 ms to 326.7 ± 44.3 ms, $p = 0.013$).

Differential Diagnosis

The clinical differential of DSWPD includes an evening circadian preference without significant distress or impaired functioning, inadequate sleep hygiene with resistance to going to bed at an appropriate time, use of sleep-disrupting drugs or substances, and/or chronic insomnia disorder. Epidemiological surveys often differentiate chronic insomnia from DSWPD via a paucity of sleep maintenance difficulties in the latter, as well as a resolution of subjective sleep quality and duration when DSWPD patients are allowed to sleep at desired times on unrestricted days [5, 8, 15–18].

Comorbidities

There are several conditions seen with increased frequency in patients with DSWPD. There is conjecture that this is at least partially related to the delayed timing of patients' circadian rhythms, either in a direct sense (e.g., genetic susceptibilities that increase the probability of both DSWPD and the comorbid phenotype) or in an indirect manner, i.e., as a consequence of occupational, academic, and/or social impairments. The condition seldom presents as a circadian misalignment in isolation, and associated comorbidities may be most challenging for clinicians.

Rajaratnam et al. [5] selected 295 participants between the ages of 18 and 65 deemed to be at high risk for DSWPD, based upon completed surveys culled from 13,844 US respondents. A comparison group of over 700 subjects was comprised of

"low-risk" non-evening types. The high-risk group (aged 31.2 ± 12.2 years) was significantly younger ($p < 0.001$) than their counterparts (40.0 ± 15.0). The authors evaluated the presence of general impairments using an online version of the Sheehan Disability Scale [19]. The high-risk cohort exhibited comparatively increased daytime impairments, including moderate, marked, or extreme disruptions in work and/or school environments (32.9% vs. 18.0%) ($p < 0.001$). In addition, absenteeism was reported in 12.2% of the high-risk group vs. 6.5% of the low-risk group ($p = 0.025$).

Likely contributing in part to the findings described above, depression and personality vulnerabilities are frequently comorbid with DSWPD [20–23]. Shirayama et al. [20] recruited 22 ICSD-diagnosed DSWPD subjects and 20 matched controls through the National Center of Neurology and Psychiatry in Kodaira, Japan. The DSWPD patients consisted of 12 men (25.5 ± 5.5 years) and 10 women (29.2 ± 5.1 years) with symptom durations of 7.1 ± 4.8 and 8.9 ± 4.1 years, respectively. No prior treatment was reported by 16 (73%) subjects (10 men and 6 women).

The two groups received three types of psychological tests, including the Yatabe-Guilford test (Y-G test) [24], the Minnesota Multiphasic Personality Inventory (MMPI) [25], and the Rorschach test [26]. The DSWPD Y-G and MMPI assessments revealed statistically significant increases in depressive symptoms. The Rorschach test results reflected decreased self-awareness of the inclination toward immediate gratification, which the authors attributed to difficulties learning from experience, perhaps perpetuated by social withdrawal from peers and/or aforementioned depressive symptoms.

Abe et al. [27] more specifically examined the prevalence and characteristics of depression in 90 Japanese ICSD-defined DSWPD patients (aged 27.1 ± 9.2 years) recruited from an outpatient sleep clinic. Symptoms were assessed by the Zung self-rating depression scale [28], and raw scores were divided into four severity levels, as described by Barrett et al. [29]. Sixty-four percent of patients had depression scores in the moderate to severe range (much higher than the general population [30, 31]), with diurnal variation, sleep disturbance, fatigue, and psychomotor retardation reported most often as accompanying symptoms.

Wilhelmsen-Langeland et al. [21] used the NEO-PI-R (Neuroticism, Extroversion, Openness-Personality Inventory-Revised) [32] to assess personality traits among 40 Norwegian ICSD-diagnosed DSWPD patients (20.7 ± 3.1 years) compared to 21 age-matched controls, all recruited through local school advertisements. The DSWPD group scored higher in neuroticism (anxiety and depression) and lower in conscientiousness (dutifulness, achievement striving, and self-discipline). The authors' interpretation was that the requirement to arise from bed early in the morning, with attendant sleep deprivation, increased the risk for interpersonal conflicts. Internalization of these conflicts lowers self-esteem and sense of personal competence, thereby reducing the capacity to enforce self-discipline. The strongest area of deviation from normative values was demonstrated

in conscientiousness, with 62.5% of DSWPD patients scoring low or very low. This NEO-PI-R facet is a known predictor of poor treatment compliance, which led the authors to conclude that effective treatments must incorporate motivational interventions.

Epidemiology

DSWPD prevalence reports vary considerably [33], but the condition clearly occurs most commonly among adolescents and young adults. United States DSWPD prevalence studies have only been published in abstract form and are therefore not included within.

Ohayon et al. [34] described an adolescent DSWPD prevalence of 0.4% in France, Great Britain, Germany, and Italy. The sample was composed of a total of 1125 adolescents aged 15–18 years of age. Each country conducted separate surveys using the same methodology from 1993 to 1997. The latest census figures were used to build representative samples according to age, gender, and geographic distribution. Diagnostic interviews were conducted by telephone using the Sleep-EVAL computer program, a level 2 expert system capable of formulating diagnostic hypotheses and validating through further questions. Importantly, the European schools documented later school start times than most in the United States, which would serve to decrease prevalence estimates in comparison to American counterparts [35].

Lovato et al. [8] reported on 374 Australian adolescents (aged 15.6 ± 1.0 years) recruited from eight schools in urban Adelaide. Subjects completed 7-day sleep diaries in association with wrist actigraphy. While 51.9% of their sample met one ICSD criterion and 14% met two criteria, only 1.1% met full DSWPD criteria. Hazama et al. [36] gave a self-administered questionnaire of their own composition to a total of 4971 Japanese junior high (1240), senior high (1205), and university students (2526) from rural areas. Questions were based on ICSD diagnostic criteria (1997) [15] but with a symptom duration of at least 6 months. Analyses provided an overall DSWPD prevalence estimate of 0.48%, which increased to 1.66% in the subgroup of university students.

Sivertsen et al. [16] surveyed 9338 Norwegian adolescents aged 16–18 (17.8 ± 0.8 years). Questions approximated ICSD criteria [33] and incorporated school attendance assessments. The overall DSWPD prevalence rate was 3.3% and those afflicted had significantly higher rates of school non-attendance than their non-afflicted counterparts ($p < 0.001$). Danielsson et al. [37] randomly sent questionnaires to 1000 young people in urban Sweden aged 16–26 years, of whom 671 (ages 21.8 ± 3.1 years) responded. The questionnaire approximated DSM-5 (*Diagnostic and Statistical Manual of Mental Disorder*, Fifth Edition) [38] rather than (very similar) ICSD criteria [4, 33]. Twenty-seven participants (4%) met DSWPD criteria.

The prevalence rates cited above range from 0.4% to 4.0% in adolescents and young adults. Differences may relate to numerous factors including the methodology of the surveys, school start times, and the geographical representation of the samples, including urban or rural environments.

Pathophysiology

A delay in circadian phase correlates with the beginning of puberty in both humans and other mammalian species [39–50], although in humans a combination of physiology and behavioral influences is readily apparent. There is also evidence [39, 42, 46] to support a decreased response to homeostatic sleep drive during human adolescence, as well as a decreased sensitivity to the phase advancing effects of morning light and an increased sensitivity to the phase delaying effects of evening light [47, 48]. This latter finding is also seen in pubertal mice [49, 50] and relies on the presence of gonadal hormones. All of these factors serve to facilitate adolescents' typically later times of sleep onset and offset.

Although one may envision the phenotype of DSWPD as an extreme manifestation of one or more of these phenomena, the precise etiology is unclear. Some studies [51, 52] describe longer circadian period lengths among DSWPD patients, making it harder to maintain non-delayed entrainment within the 24-hour light/dark cycle. Micic et al. [51] recruited participants through advertisements posted at universities across Adelaide, Australia. Six DSWPD participants (mean age 22.0 ± 3.3 years) and an age-matched comparison group of 7 "good sleepers" completed the protocol. Circadian period length (tau) was determined by an ingestible core body temperature capsule that transmitted readings every minute during a 78-hour experimental routine [53]. The DSWPD participants had a mean tau of 24 hours and 54 minutes (SD = 23 minutes), while the control group had a mean tau of 24 hours and 29 minutes (SD = 16 minutes) ($p = 0.04$).

Though not directly addressed in this chapter, it is important not to neglect the numerous external factors that may contribution to the induction, exacerbation, or perpetuation of DSWPD, including behavioral [20, 40, 54, 55] variables, reduced parental influence on bedtimes [56], the evening use of blue screens and social media [57], and part-time employment after school [58]. More direct maladaptive sleep-related behaviors are also prominent, such as markedly later rise times on weekends [59], which can lessen the homeostatic drive that favors an earlier sleep-onset time and mask the advancing effects of morning light. A key issue for practitioners is to disentangle the myriad internal and external factors contributing to sleep/wake delays.

Genetic Factors

Genetic screening for clock gene polymorphisms is not presently commercially available, but has the potential to aid our understanding of the pathophysiology of DSWPD [60–65]. The circadian rhythms of mammals involve a highly complex set

of interactions with a transcriptional and translational feedback loop of clock component genes [66, 67]. What follows is a simplified model to allow a preliminary understanding of relevant genetic anomalies and their putative roles in DSWPD (Fig. 6.1).

The clock gene encodes a transcriptional regulatory protein, CLOCK, which forms a heterodimer in the cytoplasm with another protein called BMAL-1 (Brain and Muscle Aryl hydrocarbon Receptor Nuclear Translocator-Like-1 protein) [67]. The bmal-1 gene is rhythmically transcribed out of phase with period (per) and cryptochrome (cry) genes. The CLOCK/BMAL-1 heterodimer is able to pass into and accumulate in the nucleus of the cell until it is degraded by phosphorylation. In the nucleus, this heterodimer activates the transcription of the per and cry genes with slow production of their respective proteins. These proteins form CRY/PER heterodimers in the cytoplasm, which then translocate into the nucleus, causing inhibition of the CLOCK/BMAL-1-induced transcription of the per and cry genes, until phosphorylation/degradation prevents further translocation. The cycle then starts anew as fresh CLOCK/BMAL-1 heterodimer induces a new round of gene transcription. This transcription-translational feedback loop is completed in slightly over 24 hours.

There have been several studies [60–65] looking at polymorphisms or mutations in this system. Ebisawa et al. [63] reported an association of per3 polymorphisms with DSWPD in Japan. Archer et al. [64] reported an association of a length polymorphism in the same with evening preference and DSWPD. Most recently, Patke et al. [60] described a family of Turkish descent with familial DSWPD transmitted in

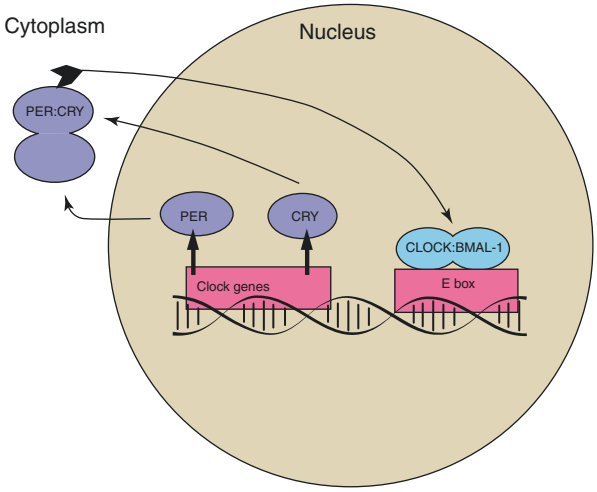

Fig. 6.1 A simplified model of the cryptochrome (cry) and period (per) genes and their role in the ~24-hour translational/transcriptional-based feedback oscillator that comprises the molecular circadian clock. The CLOCK/BMAL-1 heterodimer binds to the E-box promoter of the clock genes, activating (+) the production of CRY and PER proteins. These proteins leave the nucleus, combine into a heterodimer in the cytoplasm (if not degraded by phosphorylation), and return to the nucleus and accumulate, inhibiting (−) the CLOCK/BMAL-1 activation of cry and per gene transcription and completing the feedback loop

an autosomal dominant fashion. Afflicted individuals demonstrated an adenine-to-cytosine point mutation in the cry1 gene, which caused a 24-amino-acid skip in the production of altered CRY1 protein. Fibroblast cultures revealed a gain of function, leading to increased nuclear localization and enhanced inhibition of the CLOCK/BMAL-1 heterodimer's activation of gene transcription. This led to a delay in the re-initialization of the transcriptional and translational feedback loop and lengthening of the circadian period. Indeed, the measured circadian period of one subject was prolonged at 24.5 hours [60], compared to a normal control value of 24.2 hours [68]. Further genetic screening of the family showed no other changes in clock-related genes. The authors looked at available human databases of human genetic variations and found the frequency of the cry1 mutation to be up to 0.6%, consistent with the overall reported frequency of DSWPD. This finding is also of potential interest from a comorbidity standpoint, as both Soria [69] and Hua [70] reported over representation of cry1 polymorphisms in patients with major depression.

Treatment

Therapeutic circadian-based interventions for DSWPD consist primarily of post-awakening light therapy and/or strategically timed melatonin. Cognitive behavioral therapy for comorbid insomnia (CBT-I) commonly accompanies these treatments. Large-scale randomized controlled trials for DSWPD are lacking, as illustrated by the American Academy of Sleep Medicine's (AASM) most recently published circadian rhythm sleep-wake disorder practice guidelines [71]. Affirmative findings are described below, with notation of those studies that were not included in the AASM's systematic evidence review. Negative findings were plentiful due to the rigorous GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system employed. As a case in point, there was insufficient evidence to endorse post-awakening light treatment as monotherapy. While the use of GRADE should ultimately propel greater quality clinical research, clinicians will invariably need to employ less rigorously studied interventions and to extrapolate well-described scientific data into clinical practice to satisfactorily address patients' needs. Patient frustrations leading to noncompliance are common, as responses are not rapid and effects are often modest. Clinicians should therefore be prepared to exhibit patience, to provide encouragement, and to adopt a long-term view required for management of chronic illnesses.

Combination Light Therapy Studies

Gradisar et al. [72] *combined* post-awakening light therapy with cognitive behavioral therapy for insomnia (CBT-I) over a period of 8 weeks. The study included 23 adolescent DSWPD patients (ages 14.7 ± 1.7 years) who were compared to an age-matched wait list group. Sleep diaries were used to ascertain subjective sleep parameters.

Upon arising from bed, the participants were exposed to either natural sunlight or a 1000 lux broad-spectrum lamp, for 30–120 minutes. In counterclockwise increments of 30 minutes per day, the participants advanced to a target time of 6:00 AM. At that point, light therapy was discontinued, and the participants were encouraged to maintain the earlier rise time. This occurred in conjunction with six 45–60-minute sessions of CBT-I with a clinical psychologist, with significant parental involvement. At the end of the trial, statistically and clinically significant differences (the latter predefined by the AASM practice parameter Task Force) were noted in the active treatment group on school nights versus the wait list group in regard to total sleep time (8.1 ± 0.6 hours vs. 6.9 ± 1.1 hours) and initial sleep latency (22.2 ± 12.8 minutes vs. 65.3 ± 42.0 minutes), respectively. Moreover, the dropout rate in the treatment group was more favorable than that of the wait list group (11.5% vs. 26.1%, respectively). Six-month follow-up assessments revealed durable responses.

A separate combination treatment study was published subsequent to the AASM practice parameter's availability and, as such, was not subject to the same evidence-based review. Danielsson et al. [73] conducted a two-phase study of light therapy (LT) and CBT-I in individuals aged 16–26 years. The 57 participants were randomized into two groups. In the initial 2-week phase, both groups were exposed daily to 30–45 minutes of 10,000 lux bright white light post-awakening. Eleven individuals (19%), roughly split between the two groups, were either noncompliant or intolerant of treatment, leaving 46 (81%) to proceed to the second 4-week phase of LT + CBT-I versus LT alone. Within the former group, 4 weekly 90–120-minute CBT-I sessions were conducted by a clinical psychologist.

Sleep diaries were used to measure sleep onset and offset. The first 2-week phase showed statistically significant improvements from baseline among all participants (advances in sleep onset from 3:10 AM ± 1:23 to 1:19 AM ± 1:26 and 2:56 AM ± 1:28 to 1:08 AM ± 1:00 and in sleep offset from 10:27 AM ± 1:57 to 8:09 AM ± 1:22 and 10:22 AM ± 2:05 to 8:14 AM ± 0:55 among pre-CBT-I + LT combined and LT-alone groups, respectively). During the subsequent 4 weeks of treatment, five out of the six dropouts originated from the combined CBT-I + LT group, and there were no further statistically significant sleep-onset or offset changes. The relatively higher dropout rate in the CBT-I + LT group is difficult to reconcile with that observed with the Gradisar study. The addition of CBT-I did not confer additional benefit versus LT alone overall, although participants were older than those in the Gradisar study (perhaps requiring less external influences). Neither the Gradisar nor the Danielsson study was designed in a manner that allowed one to extricate the individual benefits of LT and CBT-I.

Adverse Effects Associated with Light Therapy

No studies have been done that specifically address potential harms of light therapy in patients with DSWPD, but no serious adverse effects have been reported. In the Cochrane Systematic Review for the treatment of nonseasonal depression, Tuunainen and colleagues [74] found that hypomania was the sole adverse effect

more common among patients receiving light therapy versus controls (Relative Risk 4.91 [CI 1.66–4.46]). Nevertheless, light therapy has been safely used for the treatment of bipolar depression, with careful monitoring [75]. Other minor, but commonly described adverse effects include eye strain, nausea, and agitation, which all tend to spontaneously remit. Treatment-emergent headaches also commonly remit [76], but light therapy can induce migraines in approximately one-third of those susceptible [77]. Although commercially available products do not emit ultraviolet light, patients with eye disease and/or those using photosensitizing medications should only use light therapy with periodic ophthalmological and/or dermatological monitoring of the underlying condition [76, 78, 79]. Reassuringly, one study reported no changes in extensive ophthalmologic examinations among seasonal affective disorder patients without preexisting conditions after up to 6 years of daily use in the fall and winter months [78].

Melatonin

Two adult studies of exogenous melatonin performed by the same investigators [80, 81] demonstrated substantial select polysomnography-measured benefits in sleep parameters (total sleep time, initial sleep latency), but an affiliated circadian phase marker was not employed. The Rahman study [81] (n = 20, randomized, double-blind, placebo-controlled, crossover design, mean age 30.8 ± 12.4 and 35.6 ± 14.0 years for females and males, respectively) utilized a 5 mg melatonin dose administered between 7:00 PM and 9:00 PM for a period of 28 days. The Kayumov study [80] (n = 20, same design/age distribution) used the same dose, but scheduled it at 7:00 PM the first week and between 7:00 PM and 9:00 PM the second and third weeks (according to subjects' preferences) with a consistent time during the fourth week (average chosen time 9:00 PM). The most definitive results were obtained from an analysis of a subset of patients without comorbid depression from the Rahman study (n = 12, increased total sleep time = 56.00 minutes [CI 48.51–63.49]). Initial sleep latency was assessed with the same subcategorization. Among the subgroup with comorbid depression (n = 28), sleep latency decreased by 43.52 minutes [CI −34.45 to −52.60]. Among the nondepressed subjects (n = 12), sleep latency decreased by 37.70 minutes [CI −31.75 to −43.65].

One AASM-reviewed randomized, placebo-controlled double-blind study contained solely pediatric DSWPD patients, ranging in age from 6 to 12 years [82]. The three active treatment groups received melatonin at dosages of 0.05 mg/kg, 0.1 mg/kg, and 0.15 mg/kg, with respective mean doses of 1.6 ± 0.4 mg (n = 16), 2.9 ± 0.9 mg (n = 19), and 4.4 ± 1.0 mg (n = 18). The placebo-controlled group consisted of 17 patients. The duration of treatment was six nights, with instructions to consistently take melatonin 1.5–2.0 hours prior to habitual bedtime (unclear if equivalent to habitual sleep-onset time), with consistent nightly timing. The data of 64 participants were utilized for actigraphy/sleep-related analyses. With

respect to AASM Task Force-defined critical outcomes, sleep-onset time favorably advanced in comparison to placebo among the 0.15 mg/kg group only (mean difference -42.77 minutes [CI −21.77 to −63.78]). Nevertheless, sleep latency improved among all three groups (statistical and Task Force-defined clinically significant differences) in comparison to placebo in order of increasing dosage (mean difference −38.39 minutes [CI −18.24 to −58.53], −44.24 minutes [CI −24.04 to −64.44], and −43.80 minutes [CI −24.06 to −63.54], respectively). A positive relationship between DLMO phase advances and an earlier circadian time of administration (TOA) was described with no differences between the various melatonin dosage groups. No advantages between clock determined TOA versus circadian determined TOA were demonstrated in relation to sleep-onset and initial sleep latency times.

Two randomized, placebo-controlled studies by another group of investigators examined the use of melatonin for DSWPD among children/adolescents with various psychiatric comorbidities (all were diagnosed with attention deficit hyperactivity disorder) [83, 84]. Participants aged 6–12 years received fast-release melatonin for 4 weeks at dosages of 3 or 5 mg at either 6:00 PM or 7:00 PM. The more recent study [83] based dosage on weight (3 mg if <40 kg; 5 mg if >40 kg at 7:00 PM) while the earlier protocol [84] uniformly provided 5 mg at 6:00 PM. Combined analyses (n = 132) revealed an advance in DLMO of nearly 1 hour in comparison to placebo (mean difference −54.22 minutes [CI −31.67 to −76.78]). Actigraphically assessed sleep-onset time (n = 130) also advanced (mean difference −36.57 minutes [CI −16.96 to −56.18]). Other actigraphically derived sleep parameters were obtained only in the more recent study (n = 105), but failed to detect statistical and/or Task Force-defined clinically significant changes. Subjective assessments in the earlier study failed to demonstrate significant differences in sleep parameters [84].

Subsequent to publication of the AASM Practice Parameters, Sletten et al. [85] tested the efficacy of 0.5 mg of immediate-release melatonin for ICSD-defined DSWPD in an Australian multicenter trial (n = 116). Inclusion criteria mandated that subjects have a physiologic delayed circadian phase, defined by occurrence of the DLMO within 30 minutes of their habitual bedtime (HBT) or any time thereafter. Participants were randomized to melatonin (n = 54; 29.94 ± 9.63 years) or placebo (n = 50; 28.88 ± 10.46 years), with instructions to take the capsule 1 hour before HBT. Sleep diaries and actigraphy were utilized throughout the 4-week treatment period. On average, the participants took the study drug on 21.11 ± 3.18 nights, and only 5% took drug every night. Posttreatment DLMO values did not reach statistical significance. Actigraphy data demonstrated statistically significant improvements in the melatonin group for sleep-onset latency (95% CI −9.68 [−16.69 to −2.67]minutes) (p = 0.007), sleep efficiency (95% CI 2.72 [0.59–4.86] %) (p = 0.013), and sleep-onset time (95% CI −0:29 [−0:54 to −0:04 hours:minutes) (p = 0.023). The sleep diaries revealed similar findings, albeit with additional improvements in sleep offset time (95% CI −0:35 [−1:00 to −0:11] hours:minutes (p = 0.005).

The astute reader will note demonstration of successful sleep-related outcomes without changes in the circadian phase marker and vice versa, both within the studies reviewed above and elsewhere [71]. Related, the use of chronobiotically timed

melatonin was given a weak endorsement within the AASM practice guidelines [71]. Nonclinical scientific evidence among healthy individuals suggests that lower doses of melatonin than were used in the cited studies (with the exception of the Sletten study [85]) may actually be more effective than higher doses, however, possibly because the latter exerts effects on both phase advance and phase delay portions of the phase response curve.

Moreover, since phase response curves for a melatonin dose of 0.5 mg (healthy adult populations) show maximal phase advances when taken approximately 10–12 hours prior to the mean midpoint of sleep on "free" or unrestricted sleep nights (or 6–8 hours prior to the mean sleep-onset time on free sleep nights) [86], timing may have been problematic in these studies, which in some instances may have resulted in melatonin functioning as an hypnotic rather than a chronobiotic.

When taken correctly and consistently, low-dose melatonin can reliably affect a 90 minute (±30 minutes) phase advance. Once a new steady-state circadian phase has been achieved (after 1–2 weeks), the midpoint of sleep on free days can be recalculated, and the dosing time adjusted. Additional stepwise advances might be necessary until satisfactory results are achieved [87]. While maintenance protocols have not been established, clinical practice supports subsequent use of melatonin at a fixed time, with earlier dosing if sleep consistently occurs later than desired and later dosing if sleep consistently occurs earlier than desired [88]. Similarly, the timing of post-awakening light therapy can be adjusted with the same logic. If spontaneous awakenings occur earlier, the timing of light should change accordingly, until the desired time of awakening is achieved. One can then continue to administer light at a fixed time. A trial off of melatonin and/or light can be pursued with rigid adherence to the desired sleep/wake schedule, with a low threshold to return to treatment if symptoms recur. At least three laboratory-based studies among healthy adults describe a synergistic effect (with respect to circadian phase advances) when strategically timed light and melatonin are used together [89–91], but there are no clinical studies to definitively substantiate this practice [92, 93]. Further investigations are required to determine which timing and dosage of therapy (or therapies) result in the best outcomes for those with DSWPD.

Adverse Effects Associated with Melatonin

Melatonin is considered a dietary supplement and is therefore not subject to the scrutiny afforded to the United States Food and Drug Administration (FDA)-approved medications. Concerns have been raised about the purity of available formulations, as well as the reliability of stated doses per tablet. Formulations that are United States Pharmacopeia Convention Verified can be considered the most reliable in this regard. In general, melatonin is associated with a lack of reported serious adverse effects [94–98]. A review by the National Academy of Sciences stated that short-term use of ≤10 mg/daily (higher than typical chronobiotic doses) appears to be safe in healthy adults but recommended caution in children/adolescents and

women of reproductive age (see further below). Adverse effects such as headaches, somnolence, hypotension, hypertension, gastrointestinal upset, and exacerbation of *alopecia areata* have been reported at higher melatonin doses in healthy adults, and the same effects have been reported at lower doses among those with relevant pre-existing conditions. Melatonin has also been associated with an increase in depressive symptoms [99], and caution is advised when prescribing to patients taking warfarin and to patients with epilepsy, as a result of various case reports submitted to the World Health Organization [95]. A recent publication described impairment in glucose tolerance among healthy women [100] subsequent to acute melatonin administration.

Studies that address long-term effects are scarce, as are studies that specifically involve pediatric/adolescent populations. A randomized, placebo-controlled trial that investigated the toxicology of a 28-day treatment with 10 mg melatonin (solely comprised of healthy male adult participants) revealed no group differences with respect to adverse effects on polysomnography, subjective sleepiness, numerous clinical laboratory examinations, or other subjectively recorded events [101]. Similarly, in a meta-analysis that reviewed controlled trials with melatonin ($n = 10$ studies, >200 subjects) with use for ≤3 months, there were few reports of adverse events [99]. A long-term follow-up study of pediatric patients with DSWPD + attention deficit hyperactivity disorder who utilized melatonin doses up to 10 mg (mean follow-up time of approximately 4 years) detected no serious adverse events in serial interviews with the children's parents, and 65% of participants continued to use the medication daily [102]. A follow-up open-label prospective study of subjects with neurodevelopmental disabilities comorbid with DSWPD who received controlled-release melatonin (max dosage 15 mg) up to 3.8 years similarly described no adverse events [103, 104]. Patients and caregivers are nevertheless frequently wary to use this supplement, due to concerns related to potential adverse effects on growth hormone regulation (10 mg dose) [105] and on reproductive function/development (3 mg dose) [106]. Possibly relevant to the latter concern, Tanner (pubertal) stages [107, 108] were assessed serially in a questionnaire-based study involving children/adolescents (mean duration ~3 years), in an effort to compare pubertal development among those using melatonin (mean dose ~3 mg) during prepuberty to non-melatonin users in the general Dutch population (controls) [109]. No significant group differences were detected.

Less Explored Interventions

Creative and off-label interventions are often required for DSWPD. Esaki et al. [110] reported a pilot study of blue light-blocking glasses for evening use in DSWPD. They conducted an open-label design of seven patients (five males, mean age 18.11 ± 3.18 years) who completed the 4-week trial. The participants completed baseline actigraphy and DLMO measurements during Week 1 and at the end of the trial. During Weeks 2–4 the participants wore glasses that blocked wavelengths

below 530 nm from 9:00 PM until bedtime and removed the glasses only in the dark. The DLMO showed an advance of 78 minutes (95% CI: −34 to 183 minutes) though this was not statistically significant ($p = 0.145$). Actigraphy data showed a significant mean advance in sleep-onset time of 132 minutes (95% CI: 13–252 minutes) ($p = 0.034$). This small study provides some preliminary evidence that "blue-blocker" glasses (which are already commercially available) may be beneficial for DSWPD patients.

There are isolated reports regarding the use of hypnotics in DSWPD (typically as an adjunctive treatment with chronotherapy), but there is insufficient rigor in methodology for purposes of evidence analysis [111, 112]. Two reports describe DSWPD patients' resistance to the effects of traditional hypnotics [113, 114]. Nevertheless, a laboratory-based study that imposed a 4-hour phase advance on healthy subjects described sleep-related benefits (polysomnographic and subjective measures) with zolpidem [115]. The off-label use of neuroleptic medications has also been reported. Omori et al. [116] described an open-label, flexible-dose, 4-week trial of "low dose" aripiprazole in 12 adult subjects, the majority of whom suffered from comorbid depression and were on complex medication regimens, including combinations of antidepressants and mood stabilizers. Evaluations included 1 week of prescreening and assessments every 1–2 weeks. Sleep diaries revealed significant advances in sleep onset [1.1 hours ± 1.2 ($p = 0.021$)] and sleep offset [2.5 hours ± 1.3 ($p = 0.001$)] and a decrease in total sleep time [1.3 hours ± 1.4 hours ($p = 0.018$)]. The latter was viewed as favorable in this particular study as a countermeasure for sleep inertia. None of these trials employed circadian phase markers.

Finally, modafinil and armodafinil are widely used as wake-promoting agents for numerous FDA-approved indications, including daytime sleepiness from shift-work disorder [117]. It may be used off-label for occasional adjunctive use in patients with DSWPD, although there are no studies that can support or refute this indication.

Conclusions and Future Directions

This chapter presents DSWPD clinical features, diagnostics, comorbidities, epidemiology, pathophysiology, genetics, and available treatment modalities. Circadian-based basic science developments continue to outpace clinical research pertaining to CRSWDs. The recently published (2015) AASM practice guidelines [71] point out these deficiencies and may serve as a roadmap for future studies that will propel higher-quality, more sophisticated therapies.

Generally speaking, larger more rigorously designed studies (randomized placebo-controlled trials) with ICSD-3 defined DSWPD [4] are required, and replication of results from separate centers is essential. More specifically, future studies could advance the field by including detailed therapeutic information, such as the method and means of treatment delivery (e.g., protective eyewear vs. volitional avoidance of light, light therapy intensity/wavelength/proximity, continuous vs. pulsed light administration [including gradually vs. abruptly changing illumination] [118], melatonin

formulation, relationship of treatment timing with respect to a defined physiologic circadian phase marker or other sleep parameter, inclusion/exclusion of prescribed sleep/wake schedules or other behavioral interventions, and study environment [laboratory vs. non-laboratory]). Future research should also address the "dose" of light utilized including lux level, duration [119], as well as season [120] and other environmental factors that affect overall light exposure history [121].

Field-based studies are sorely needed. While it is necessary to extrapolate information gleaned from healthy subjects in simulated settings (due to the paucity of clinical research), one must also be cautious not to let tightly controlled bench research prematurely dictate clinical treatment. As a prime example, there are currently no data to support devices that solely deliver blue short-wavelength light in the treatment of DSWPD, and two laboratory-based studies that describe no additional benefit with blue-enriched bright light [122, 123], despite the fact that these wavelengths have been identified as especially important for circadian phase resetting in nonclinical experiments [124].

From the standpoint of outcomes, similar *clinically relevant sleep-related* measures will be required for inter-study comparative purposes (polysomnography vs. actigraphy vs. subjective reports, and physiologic or non-physiologic circadian markers). Systematic measures of treatment compliance are also required to accurately inform clinical practice. In the melatonin study performed by Sletten and colleagues [85], completers took the study drug on only 21.11 ± 3.18 nights of the 28-day trial, with an average of 5.30 ± 1.00 tablets per week. Only 5% of the participants were fully compliant/adherent and took capsules all 28 days. Reporting of such should be uniform and as objective as possible in circadian-based studies, so that readers can better interpret results (and understand their limitations). A separate strategy that has been investigated for post-awakening light therapy (for which compliance is also poor) [125] examines the bypassing of this barrier via delivery of treatment through closed eyelids (i.e., during sleep) [126–129].

Inter-study medication (e.g., melatonin) comparisons will require equivalent dosing, timing (with respect to clock time, typical sleep-onset time, or other physiologic/non-physiologic circadian marker), and treatment durations, to accurately gauge benefit. The issue of formulation may also be relevant in melatonin studies (regular vs. sustained release vs. sublingual, etc.), and one group suggested that slow exogenous melatonin metabolism could be responsible for a lack of sustained effect in select instances [130].

Taking into account melatonin safety concerns (particularly among children and those of reproductive age), future properly powered studies should be performed to identify the lowest effective melatonin dosage and duration of treatment (acute and maintenance). Long-term physiologic studies are needed to accurately ascertain any serious chronic risks, particularly as melatonin supplements are not subject to FDA oversight [131]. At least two other investigations (involving ramelteon) also suggest a potential future DSWPD treatment role for melatonin agonists [132, 133].

Related to long-term risks of circadian-based interventions in general, research is needed to determine the minimum required duration of specific treatments (or if they are required indefinitely) and/or to determine maintenance treatment schedules.

Further studies that investigate multimodal or combination therapies are needed to determine whether combinations may prove to be synergistic and to extricate independent effects of treatment modalities, so that relative successes and failures can be exploited for differing clinical scenarios. With respect to the latter point, in the previously cited Gradisar study [72] (involving adolescents with DSWPD), light therapy was discontinued (and apparently not required) once a target wake time was reached, at which time solely behavioral interventions ensued. It is not clear to what degree this treatment could be generalized to all DSWPD populations.

Demonstration of superiority (or lack thereof) of circadian versus clock-hour timing for interventions should engender studies that aim to explore demonstrable benefits of phase assessments in the clinical setting, which in turn could serve to delineate relative chronobiotic versus hypnotic effects of medications or supplements. Some of the reviewed interventions demonstrated successful sleep-related outcomes without changes in the circadian phase marker and vice versa. If the importance of circadian phase timing of administration is demonstrated, it will be necessary to determine light and melatonin phase response curves for adult and pediatric populations afflicted with DSWPD (as they may differ from normal populations [86, 134]). Complicating matters, alterations in phase relationships between the circadian timing system and the timing of sleep among those with DSWPD could impact the ability of interventions to exert benefits, even with knowledge of the pertinent phase response curves. For example, longer intervals from various endogenous melatonin parameters [135] and core body temperature minima [136–138] to sleep offset have frequently been described among adult patients with DSWPD as compared to controls. However, this finding has not been demonstrated among protocols in which subjects are forced to maintain a more conventional sleep/wake schedule [139–141], suggesting that this observation may simply be a consequence of longer habitual total sleep time. Greater elucidation is required. On a separate note, effective treatments may need to address concomitant impairment of homeostatic sleep processes in DSWPD and among adolescents in general [46, 142]. Whether hypnotics have a role in this setting deserves to be further explored [115].

This chapter reflects the biological underpinnings associated with DSWPD. Studies are needed to investigate and understand predominant exogenous and endogenous contributors to the development and perpetuation of this condition, so that different subtypes (and possibly different treatment/prophylactic regimens) can be identified. In the case of adolescents/young adults and, to a lesser degree, other adults, numerous exogenous factors, such as increased autonomy with respect to sleep time, employment, and involvement in extracurricular activities, have been identified as variables contributing to the generally observed delay in sleep/wake patterns [34], but have not been studied among adolescent DSWPD cohorts specifically [143, 144]. Additionally, repeated exposure to frustrations at not being able to fall asleep at a desired time can lead to the development of a concomitant conditioned insomnia, which can perpetuate sleep difficulties. Exposure to indoor lighting during evening hours [145–148] and/or delays in weekend wake times [59, 149, 150] have also been implicated as contributors to persistently delayed sleep/wake times, but have not been specifically implicated in adolescent DSWPD [151]. Some

have urged that school lighting environments be optimized for maximal circadian benefits [152]. Identification and manipulation of exogenous variables in trials of DSWPD may prove fruitful.

The associated development of clinical profiles would enable clinicians to better ascertain which patients might respond to suggested treatments, and related research is encouraged. In the Gradisar study [72] of adolescents with DSWPD, barriers to successful outcomes with light therapy included school nonattendance, unrestricted sleep during vacation periods, and (not surprisingly) amotivation. Patients fitting this profile are perhaps better suited to less complex interventions. In a separate study involving young adult subjects with DSWPD and non-24-hour sleep-wake rhythm disorder receiving melatonin, a higher response rate correlated indirectly with a shorter habitual total sleep time, as well as a later age of onset [153]. Information such as this may eventually allow clinicians to optimally tailor treatment.

In select cases, accommodation to a DSWPD patient's circadian preference may be most practical, and further studies examining implementation of such schedules are desirable. Believing that some DSWPD cases are refractory to treatment, Dagan and Abadi [154] recommended foregoing therapy and instead urged implementation of rehabilitation and accommodation to the preferred sleep/wake schedule in select instances, including support for disability from duties that require strict sleep/wake schedules, and encouragement to pursue endeavors with more flexible scheduling. The benefits of such accommodation were demonstrated in a separate military-based study, with evidence of superior performance and mood among those enabled to adapt a relatively delayed sleep/wake schedule, which correlated with increased total sleep time [155]. A later school start time may be sought for adolescents, if practical and available. This intervention alone can significantly increase total sleep time and mitigate associated impairments [156–161]. This topic is reviewed authoritatively in a separate chapter.

In sum, although much work remains, significant progress has been made in the recognition/treatment of DSWPD since the inception of Sleep Medicine as a distinct medical discipline. The aim of this chapter is to provide a framework for clinicians to make properly informed treatment decisions, with the additional hope that it will serve as an impetus to address clinical research deficiencies, and promote novel inquiries for treatments of this challenging and interesting condition.

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