Delayed Sleep Phase Syndrome: Pathophysiology and Treatment Options

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Abstract: This paper presents a comprehensive review of delayed sleep phase syndrome (DSPS), a circadian-rhythm sleep disorder thought to result from the endogenous circadian pacemaker being “stuck” at a later-than-normal phase, relative to the desired sleep-wake schedule. A full understanding of this disorder is best appreciated from the context of shared modulation of sleep and wakefulness via sleep homeostatic and circadian systems. Typically emerging during adolescence, DSPS comes to clinical attention much less often than prevalence estimates would suggest, perhaps due to underrecognition by clinicians and misattribution of symptoms. Several treatment modalities have been suggested, including phototherapy, chronotherapy, and exogenous melatonin administration. However, caution is raised for the reason that more than 20 years after its initial description in the literature, the basic pathophysiology of DSPS remains poorly understood, as observed in the 2003 National Sleep Disorders Research Plan. Challenges for future research include elucidating the exact sleep homeostatic and circadian contributions to the disorder, improving the objective verification of this diagnosis instead of relying only on self-report information, and conducting treatment research aimed at determining efficacy, effectiveness, and mechanism or mechanisms of action.

Key Words: sleep, circadian rhythm, melatonin, body temperature, insomnia

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INTRODUCTION

“…EARLY TO BED, AND EARLY TO RISE…”1 IF THIS FOLK WISDOM WERE TRUE, THIS WOULD BE UNFORTUNATE INDEED FOR PATIENTS WITH DELAYED SLEEP PHASE SYNDROME (DSPS).

There are several recent reviews of DSPS or all of the circadian rhythm sleep disorders.2-6 This review begins with a summary of what is known about sleep homeostatic and circadian modulation of sleep and wakefulness. The following sections review the diagnostic procedures and prevalence data. Next is a review of factors suspected in the pathophysiology of DSPS. The major treatment modalities for DSPS are outlined and supported from the literature. The review concludes with recommendations for future research to benefit our knowledge of the etiology of and treatment for DSPS.

Sleep Homeostasis and Circadian Timekeeping

An understanding of the circadian sleep disorders such as DSPS requires appreciation of the fundamental processes that modulate the timing and structure of sleep and alertness. Although likely not offering complete explanatory power, the 2 best-studied processes of sleep-wake regulation are the sleep homeostatic process and the endogenous circadian timekeeping system.

The sleep homeostatic process travels under various aliases in the literature. Included among the list are the titles sleep-wake homeostat, sleep homeostasis, and Process S. Using the name Process S,7 Borbély and colleagues modeled the buildup of sleep homeostatic pressure during a normal bout of wakefulness as a roughly linear process. Under conditions of extended wakefulness, such as after a night of missed sleep, Process S is thought to take on a more saturating exponential function. Similarly, the satiation of sleep homeostatic drive under conditions of normal sleep timing show the greatest abatement during the first few hours of the sleep episode, reaching a near asymptote during the second half of the sleep episode. Thus, it can be concluded that were there a homeostatic process alone, sleep initiation would be progressively more and more difficult to resist across a normal 16-hour bout of wakefulness, and it might be unlikely that one could avoid accidental sleep onset after perhaps 6 to 8 hours of sustained waking. However, sleep maintenance would not logically be permitted for the full duration of a habitual 8-hour sleep episode, as homeostatic pressure would be largely diminished after the first half of that desired sleep episode.

An endogenous circadian timekeeping system, found in essentially every animal species studied to date, is the second fundamental modulator of sleep and wakefulness. Human studies have documented that in addition to exerting a regulatory effect on such internal processes as core body temperature, cortisol and melatonin secretion, and TSH release, the circadian system actively promotes both sleep and wakefulness at different parts of its cycle.3 During the latter half of the habitual waking day, wakefulness is actively promoted. The maximal level of wake promotion occurs several hours prior to habitual bedtime, earning the varied nicknames of the forbidden zone for sleep4 and the wake maintenance zone.9 During the habitual sleep episode, the circadian system switches over to active promotion of sleep, reaching a maximum drive at and just following habitual wake time.4,10 This author recently derived the term “circadian sleep maintenance zone”11 for this phenomenon, and to draw a parallel to the wake maintenance zone. Under normal conditions, the pacemaker is aligned to the wake-sleep schedule by the light-dark cycle such that the trough of core body temperature occurs 1.5 to 2 hours prior to wake time and morning light exposure.

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Assumptions for Normal Sleep-Wake Timing

Taken separately, either of these processes alone would allow for some extent of consolidation of wake and sleep episodes. However, only when taken together at the normal phase relationship do these biologic processes allow for the expression of a sustained bout of 14 to 18 hours of relatively stable wakefulness and a similarly stable 6 to 9 hour bout of consolidated sleep in the adult human. There are at least 3 critical assumptions underlying this claim.

The first assumption is the presence of an intact sleep homeostatic system. In contrast to the circadian system, there is essentially little understanding of the neuroanatomic localization or neuropharmacologic and neurophysiologic substrates of sleep homeostatic drive. Although putative neurotransmitters have been put forth as mediating this process, such as adenosine13-15 or orexin,16 it may eventually be found that this system is widely distributed in the central nervous system, contributed to by myriad pharmacologic substances. Until significant research advances are achieved, it will be difficult for researchers and clinicians to assess the functional status of the sleep homeostatic system. Only quantification of slow-wave activity of the electroencephalogram has shown reasonable promise as a proxy for reflecting the satiation of sleep homeostasis during sleep.17 A related feature somewhat easier to assess is the behavioral contribution to sleep homeostasis. In other words, is the sleep homeostatic system allowed to function? One may self-select to attempt to refrain from daytime napping, saving and building up homeostatic drive for a single major sleep episode. Noninvasive measures such as prospective sleep-wake diaries and wrist actigraphic estimation of sleep and wakefulness are inexpensive efficient means of gathering these data.

The second assumption is that of an intact circadian timekeeping system. This implies the presence of strong zeitgebers or time cues (e.g., the daily light-dark cycle) from the environment to allow for stable entrainment at a normal phase relationship with the external 24-hour day.18 There must also be an intact mechanism or mechanisms allowing for transduction of zeitgeber information to the components of the endogenous circadian timekeeping system, particularly the suprachiasmatic nucleus of the hypothalamus, which itself must function properly. Finally, there must be intact output pathways from and recurrent feedback loops to the circadian timekeeping system. In the human, it is really only possible at this point to make inferences on the integrity of some parts of the circadian system. The gold-standard assessment procedure at this point is the constant routine.19,20 By controlling and evenly distributing masking influences over more than a single period of oscillation of the circadian system, one can assume the integrity of the input pathways, central pacemaker, and output pathways by finding an intact robust rhythm of core body temperature and plasma or salivary melatonin, all occurring at a relatively predictable phase in relation to the preceding wake-sleep and, hence, light-dark cycle.

Finally, a third and critical assumption is that of a normal phase relationship between the timing of self-selected sleep and wake episodes, therein linked to the starting and ending points of accumulation of sleep homeostatic pressure, and the phase of the circadian system. As mentioned above, this can most accurately be assessed with a constant routine procedure but may also be more simply estimated from the timing of the rising limb of the melatonin rhythm with the dim-light melatonin-onset protocol21 or through measurement of the entire waveform from onset to offset.22

Emergence of Circadian Sleep Disorders

With the foundation of an understanding of the independent and combined sleep homeostatic and circadian regulation of sleep and wakefulness in normal sleepers under normal conditions, the 6 circadian sleep disorders logically emerge with only minimal perturbation of sleep homeostatic and/or circadian processes. In a manner similar to the revision of the nosology from the Association of Sleep Disorders Centers criteria to the International Classification of Sleep Disorders original and revised schema,23 it may be helpful for the purpose of clarity to divide the circadian sleep disorders into extrinsic and intrinsic disorders. Time-zone change syndrome (jet lag) and shift-work sleep disorder can be understood as extrinsic sleep disorders. In both, there is a behaviorally initiated voluntary mismatch between the desired timing of the sleep-wake cycle and circadian phase. Intrinsic circadian sleep disorders presumably result from abnormal functioning of the circadian system itself or in its interaction with sleep homeostasis. Non–24-hour sleep-wake disorder is typically expressed as a slightly later sleep episode each day and is thought to be related to disruption of input pathways, keeping light-dark information from reaching the suprachiasmatic nucleus.24,25 Thus, functionally cut off from the light-dark cycle, the suprachiasmatic nucleus “drifts” to a later hour each day, expressing its intrinsic circadian period, which averages approximately 24.18 hours.26 Irregular sleep-wake disorder is thought to result from primary dysfunction of the suprachiasmatic nucleus itself, such as would be expected to occur as the result of concurrent neurodegenerative disease or central nervous system injury.23 Thus, removing the circadian promotion of sleep and wakefulness, the sleep-wake cycle becomes highly polyphasic, with multiple shorter bouts of sleep and wakefulness occurring each day and night. Advanced sleep phase syndrome is thought to result from an abnormally early phase position of the circadian cycle relative to the desired sleep-wake cycle. Last but certainly not least for the purposes of this review, is DSPS.

DIAGNOSIS OF DSPS

Diagnostic Procedures

As with all areas of clinical sleep disorders practice, making an accurate diagnosis is the first step upon which all subsequent activities will depend. As first formally described in the literature by the late Elliot Weitzman,27 and recently confirmed (for example by Watanabe et al28), patients with DSPS are thought to have an abnormal phase relationship between the circadian system and the desired sleep-wake schedule. The complaint is therefore primarily of sleep-onset insomnia when attempting to adhere to a desired, “normal” bedtime and extreme difficulty arising at a desired “normal” wake-up time. In contrast, when on vacations or in other circumstances permitting a truly ad lib sleep schedule, these patients may self-select this perhaps biologically mandated later bedtime and wake-time schedule and have no difficulty with sleep initiation, sleep maintenance, or next-day functioning. Thus, only under the constraints of a forced early bedtime and wake-time schedule does one see the expression of the disor-
nder—inability to initiate sleep until several hours beyond desired bedtime, significant difficulty arising at an earlier wake time, and impaired next-day functioning thought to be related to the resultant truncation of total sleep time in the preceding sleep episode. Impairments in quality-of-life dimensions have been reported on the Medical Outcomes Study short form, particularly for social functioning, vitality, and effect of physical state on normal activities.29

The International Classification of Sleep Disorders-Revised31 requires certain minimal criteria for a diagnosis of DSPS. These criteria can be paraphrased as follows: (1) inability to initiate sleep at the desired time and difficulty awakening; (2) delayed (late) timing of the habitual sleep episode; (3) presence of symptoms for 1 month or more; (4) when constraints permit (e.g., when not working or attending classes), the patient opts for delayed timing of the major sleep episode, which is felt to be of good quality and quantity, and can awaken from this sleep episode without difficulty, and remains on this delayed sleep-wake schedule without difficulty; (5) 2 weeks or more of subjective sleep data (e.g., sleep-wake diary) verify the presence of the delayed, habitual sleep-wake schedule.

Assessment procedures for the first 4 criteria are self-evident and can be accomplished early in the patient’s intake evaluation. Assessment of the 2-week interval of sleep-wake data is a bit more complex. Sleep-diary assessments such as these should always be filled out prospectively, to avoid errors and inaccuracies induced by poor memory, response bias, and generalization. A useful sleep diary will allow a patient to easily denote clock times for the home equivalent of laboratory “lights off” and “lights on” (for estimation of time in bed) and estimations of sleep latency, number of awakenings, time spent awake after initial sleep onset, terminal time spent awake prior to arising from bed, and total sleep time. Other critical information includes medication or other substances used to aid sleep, daytime napping, or unusual events occurring on the day preceding the sleep episode. Optimally, wrist actigraphy would be used concurrently to gain objective data on patterns of estimated sleep and wakefulness30-32 during this 2-week interval, verifying the complaint. Actigraphy has been shown to be an efficient means of measuring degree of sleep disruption or misalignment in other circadian rhythm sleep disorders (e.g.,33), can be worn well even by active adolescents,34 and can provide good data for gauging treatment response. (e.g.,35). A recent comprehensive review of the use of actigraphy is available.36

Under ideal circumstances, making the diagnosis of DSPS would involve both objective assessment of circadian phase and verification of the sleep characteristics with 2 nights of laboratory polysomnography to confirm the International Classification of Sleep Disorders-Revised diagnostic criteria 1 and 4 (from outline above). One night would schedule the sleep episode at the patient’s reported “best” late bedtime. This would verify ease of falling asleep, good sleep consolidation, and reasonable next-day functioning following an 8-hour sleep episode. The second night would be scheduled to occur at the "desired" earlier bedtime. This night would verify the presence of sleep-onset insomnia, reasonable sleep consolidation once sleep was initiated, and the presence of difficulty arising after 8 hours of time in bed. Assessment of circadian phase could be accomplished through hourly sampling of plasma melatonin. Alternatively, melatonin could be assessed through salivary levels, which was validated against blood-sampling results in a small DSPS sample.37 Due to reimbursement issues, it is unlikely that this idealized practice assessment of circadian phase and 2 nights of polysomnography will ever become accepted standard of care. Unfortunately, a quick Internet search using the keywords of “melatonin” and “assay” revealed that many web sites are already offering to sell expensive, self-pay saliva collection kits for use at home, without obvious adherence to a validated protocol likely to provide an accurate diagnosis or interpretation and treatment planning by a board-certified sleep specialist.

Prevalence

In making a diagnosis, one should be aware of the prevalence of DSPS, estimates of which vary widely by publication. The International Classification of Sleep Disorders-Revised states that perhaps 5% to 10% of patients seen in sleep clinics for a complaint of insomnia may have DSPS.23 In a population of middle-aged subjects, a recent report found the prevalence of subjective complaints of DSPS-like symptoms was found to be 3.1%.38 Multiphase questionnaires in a Norwegian population reached a prevalence estimate of 0.17%.39 A similar estimate of 0.13% was found through a combined telephone and follow-up sleep-log and questionnaire study in a sample from Japan.40 Factors between studies likely to have influenced prevalence estimates included differences in the diagnostic criteria, the self-report measures, and the subject-recruitment procedures. Given this wide range of prevalence estimates, one would expect between 360,000 and several million DSPS patients in the United States alone. It is clear that nowhere near this number of patients seek treatment at a sleep disorders center. It is possible that the underutilization of accredited sleep disorders centers stems from both lack of public awareness and insufficient training of general practice medical caregivers in recognizing the signs of circadian rhythm sleep disorders.

Differential Diagnosis

The differential diagnosis of DSPS, based on the criteria of the International Classification of Sleep Disorders-Revised requires a careful history and some prospective self-report sleep data. Paraphrased from the formal nosology,23 this is predominantly a disorder of self-diagnosis; the patients report that they cannot fall asleep until several hours or awaken until several hours later than they would prefer. Hence, when forced to go to be earlier than the biologically mandated later hour, sleep-onset insomnia is present. When forced to arise several hours earlier than biologically mandated, a complaint consistent with insufficient sleep, sleep inertia, or both is present. Sleep-maintenance problems are not thought to be common in DSPS patients. Thus, the differential includes, at a minimum, psychophysiological or conditioned insomnia, sleep-state misperception, mood or anxiety disorders, inadequate sleep hygiene, and non–24-hour sleep-wake disorder.

Psychophysiological insomnia is ruled out simply by inquiring if the patient has similar difficulty initiating sleep at a later hour and if changing the location (e.g., a hotel) and circumstance of sleep (e.g., a vacation) allows faster sleep onset at an earlier hour. If rapid sleep onset is possible at that delayed time and sleep is of sufficient duration and consolidation, psychophysiological insomnia is likely ruled out. If changing the environment or the cir-
cumberstance surrounding sleep resolves the sleep-onset problem, this suggests psychophysiologic insomnia. Suspected sleep-state misperception usually requires a single night of polysomnography to confirm the mismatch between objective and subjective data, the latter of which usually contain the report of significantly decreased total sleep time. Also, these patients report low total sleep time regardless of timing of sleep and wake. Mood and anxiety disorders must be ruled out by clinical interview, as both can cause sleep-onset difficulty. However, consideration must be given that psychopathology may certainly coexist with DSPS and other circadian rhythm sleep disorders, through perhaps it may not be causal. Inadequate sleep hygiene would also be ruled out from a clinical interview uncovering factors that could delay sleep onset, such as daytime napping, excessive intake of caffeine or caffeine too late in the day, exercising too close to bedtime, sleeping under noisy or bright conditions, or having disturbances from co-sleeping people or pets. It may not be possible to definitively rule out non–24-hour sleep-wake disorder. Several papers have reported patients possessing characteristics of this disorder and DSPS, when assessed over a long enough period of time. However, patients with non–24-hour sleep-wake disorder tend to report either a progressively delaying sleep schedule or periodically presenting insomnia (e.g., every 1 to 2 months).

POSSIBLE FACTORS IN THE ETIOLOGY OF DSPS

There is little clarity in the search for possible causes of or contributors to DSPS. As hypothesized in the “diagnosis” section, abnormal timing of sleep and wake in DSPS could be produced from an irregularity in the sleep homeostatic system, an irregularity in the circadian timekeeping system, or an alteration of mechanism or mechanisms producing the phase relationship between these 2 processes. Candidates certainly include behavior, physiology, and genetics.

It would be entirely possible to produce delayed rhythms of core body temperature and endogenous melatonin, as well as delayed nocturnal sleep onset and offset, through voluntary behavioral means alone. A high percentage of young and middle-aged adults keep later bedtimes times on weekends, leading to a phase delay by Monday morning and resultant difficulty arising to start a new work or school week. Thus, although there are data showing delayed circadian markers in patients meeting criteria for DSPS (e.g.,), the existence of a delayed rhythm does not imply that the pacemaker is “stuck” in a delayed position or that the physiology is at fault. Recent work points toward myriad psychological traits and features that may play a role in the development or maintenance of DSPS.

A physiologic basis for DSPS has been hypothesized but with varying propositions. An abnormally large delay region and/or a small advance region of the light phase response curve (PRC) (see phototherapy below) could explain a tendency to delay. A small-amplitude phase-advance region would be expected to be associated with a range of entrainment having a lower limit very near 24 hours and, hence, great difficulty making daily shifts of phase required to offset the tendency to phase delay because of an intrinsic period of oscillation slightly longer than 24 hours. An abnormally long intrinsic circadian period might also explain DSPS symptoms. Unfortunately, these statements remain hypotheses without data to support or refute them, such as confirmation of the amplitude of the phase advance region of the light PRC in DSPS patients. In terms of physiologic findings, promise comes from data suggesting an altered phase angle between the sleep-wake cycle and circadian markers such as core body temperature and melatonin. A similar finding of phase abnormality of the core body temperature rhythm was noted in sleep-onset insomniacs. There is also a finding of impaired ability to compensate for sleep loss in DSPS patients, though it is unclear if this was mediated by deficient buildup of sleep homeostatic pressure during wakefulness or an alteration in the sleep- or wake-promoting signals from the circadian system.

One line of evidence that could support the biologic basis for DSPS is the typical emergence during the second decade. As a parallel, narcolepsy typically emerges during the second or third decade and is thought to be caused in part by progressive loss of wake-promoting neurons, perhaps related to orexin/hypocretin. Thus it may be possible that there is a similar pathologic neuronal loss in DSPS that occurs over time. Support for this line of thinking comes from an increased prevalence of HLA-DR1 in DSPS patients versus normal sleepers. Curiously, also as in narcolepsy, there have been reports of the emergence of DSPS following traumatic brain injury.

As with many other areas in clinical sleep disorders, there is a search for genetic variants in patients with circadian rhythm sleep disorders of advance sleep phase syndrome and DSPS. A familial occurrence of advance sleep phase syndrome was recently reported, although the somewhat normal mean sleep-onset times of just after 9 PM and mean wake times of after 5 AM for the “affected family members” raises the question of whether or not a true circadian phase advance is present in this family. There are publications supporting and refuting the role of the 3111 CLOCK gene in DSPS. A suspected linkage of the H4 haplotype of the human PER3 gene was reported but was present in only 7 of 96 patients with DSPS. Polymorphisms of the PER3 gene may also discriminate between extreme morning and evening types. In summary, the candidate genes or genetic mutations at this point have yielded only tantalizing clues as to the underlying mechanisms of the human intrinsic circadian timekeeping system, and thus far no smoking gun has been identified for DSPS. The work of Carskadon has shed light onto normal changes in sleep and wakefulness across child development and the transition to adulthood. Her data, along with those of others, confirms that sleep duration and sleep timing are affected by social, behavioral, and biological factors. During the teenage years, children have increased competition for their waking hours from demands such as after-school jobs, homework, school extracurricular activities, and peer socializing. The progressive delay in bedtimes could be explained merely through these external factors alone were it not for the finding of delaying circadian phase tracking normal adolescent development, suggesting the additional contribution of a biologic imperative.

To summarize, there are multiple lines of evidence suggesting dysfunctions at the behavioral, physiological, and genetic levels in DSPS. However, more research investigating the pathophysiology of DSPS is needed; all 3 of these levels of analysis are suggested as “Research Recommendations” in the 2003 National Sleep Disorders Research Plan.
TREATMENT FOR DSPS

Chronotherapy

Czeisler41 proposed the first treatment for DSPS in the same year as the disorder itself was formally described by Weitzman. In the original incarnation, chronotherapy was based on the presumption that a DSPS patient had a circadian system that was stuck in a delayed position, had an impaired ability to phase advance, and was perhaps overly capable of phase delaying. Thus, to take advantage of these factors, a patient was scheduled to delay both bedtime and wake time by 3 hours, repeated daily, until rotating around the clock and the desired sleep-wake schedule was reached. At that point, rigid adherence to the desired sleep-wake schedule, 7 days per week was instructed. In this original report, chronotherapy showed robust stable realignment of the sleep-wake schedule with good long-term follow-up results.

Unfortunately, with the current understanding of light-mediated circadian-phase resetting, it is difficult to explain why chronotherapy for DSPS should be able to produce an 18- to 20-hour phase delay. Type 1 resetting (see phototherapy below) of the pacemaker might be expected to occur given the progressively delaying light-dark schedule associated with the delaying wake-sleep schedule. However, this would be likely to produce phase shifts of only about 0.5 to 1 hour under normal indoor lighting conditions,73 and the relatively larger (3 hours per day) shifts of the sleep schedule should quickly surpass the ability of the pacemaker to shift in sync. Therefore, it is unclear why DSPS patients should report an ability to sleep at the new sleep-wake schedule given that their pacemakers would not be expected to shift the desired amount, in the desired direction, in such a rapid manner. This suggests that mechanisms other than light-mediated circadian-phase shifting may underlie the efficacy of traditional chronotherapy.

In a case report, chronotherapy was successfully applied in a 10-year-old with a previous diagnosis of attention deficit disorder, resulting in improvement in total nocturnal sleep time as well as daytime functioning,74 raising the possibility of partial symptom overlap between these 2 conditions. Additional case reports and small-sample studies of chronotherapy exist in the literature but without enough reporting of methodology or results to offer comment. Still other studies and case reports have utilized chronotherapy in combination with other treatments (e.g., with phototherapy75) and, hence, results do not allow for discussion of outcome attributable to chronotherapy alone.

Phototherapy

Administration of bright light, or phototherapy, has been best studied to produce phase shifting in the research setting, and studies typically involve multiple steps. First, there must be knowledge of initial circadian phase, typically from measurement of core body temperature and/or plasma or salivary melatonin under controlled conditions. Second, with this information, initial phase can be compared relative to 1 of the existing light PRC.76,77 Third, using data from the dose response curve,73 the intensity or dose of artificial bright light can be matched with the position on the PRC to estimate the amount of phase shifting accomplished through phototherapy. With a single several-hour pulse of bright light, “Type 1” phase resetting is accomplished. This means that relatively small (0.5- to 2-hour) phase delays or advances can be achieved if the light is given during the beginning or end of the biologic night, respectively. However, if light of sufficient intensity is delivered on subsequent days very near the crossover point between the phase advance and delay regions of the light PRC, circadian amplitude can be squelched and “critical” or “Type 0” resetting may occur.78 This allows for much larger phase shifts but of somewhat unpredictable magnitude and direction. Finally, a second determination of circadian phase is conducted to measure the outcome of phototherapy.

This phototherapy procedure is under optimal conditions in a research laboratory, with generous technologic and staffing requirements. However, there are many limitations to this idealized scenario. First, while there are good data on the relationship between light intensity and amount of phase shifting, there is no duration response curve, telling how much phase resetting is accomplished by light pulses of varying hours of duration. Second, most published circadian studies have used variants of or do not use a constant routine protocol to assess circadian phase. This leaves suspect the phase assessments, as they are highly likely to have been masked by uncontrolled or episodic changes in sleep-wake state, posture, activity level, food or water intake, or lighting conditions. The constant routine is labor intensive, expensive, and demanding on the research participant. Third, the constant routine is not currently a reimbursed medical procedure, limiting the likelihood it will be used in clinical practice. Fourth, assessment of the dim-light melatonin onset may be a reasonable proxy for measurement of a full circadian profile. However, it makes assumptions that there are not abnormalities of the duration, amplitude, or both duration and amplitude of the melatonin waveform, that the subject has a large enough amplitude of circulating melatonin to allow for determination of phase, and that one has a reasonable guess of circadian phase prior to the procedure in order to collect a minimal number of saliva or blood samples lest an entire 24-hour collection period be required. Finally, there is an assumption that DSPS patients exhibit the same dose and phase responses to light as the normal-sleeping subjects who were used to construct these functions.

Moving beyond the discussion above of idealized treatment, there have been applications of phototherapy in DSPS patients. In an early report,79 active treatment of 2 hours under 2,500 lux was administered between 6 AM and 9 AM to 20 DSPS patients versus a control condition of 300 lux. The active treatment also involved attenuation of bright-light exposure after 4 PM. Though masked core body temperature data were reported that disallow estimation of circadian phase before or after treatment, self-report data showed a better response with the active treatment relative to control. However, the lighting in the control condition was well within the range known to produce phase shifting.73 There is the additional concern that light exposure beginning as early as 6 AM in a patient with DSPS may actually fall in the delay region of the light PRC and worsen the condition. A similar early-morning phototherapy treatment has been advocated80 but, again, without knowledge of the timing of light exposure relative to the PRC. Another study81 that reported giving 5 consecutive days of phototherapy starting 1.5 hours after the core body temperature minimum, which should be in the phase advance region of the PRC, claimed to have advanced the core body temperature minimum. However, there were no data or plots of temperature given in the publication, no methodologic
details reported to know if core body temperature data were masked, and no information on how many lux of light were administered and the timing of sleep onset improved by only 1.5 hours. Phototherapy was also reported in a case study but with a rather conservative 15 minute advance of the sleep schedule per day requiring 3 weeks to complete and with even lighting that was too bright (500 lux) based on our current knowledge of phase-shifting effects of even normal indoor lighting.73

In a novel administration procedure,83 phototherapy was delivered via a light mask worn over closed eyelids in sleeping DSPS patients, but only led to a 1-hour phase advance after 26 days of treatment. Thus, it is likely that without matching treatment timing to the PRC based on individual patient circadian phase data, the potential for phase advancing was greatly attenuated, perhaps as much as the light exposure was attenuated from the closed eyelids.

Even with these limited results in studies with myriad methodologic flaws, the American Academy of Sleep Medicine has stated that phototherapy “appears to have potential utility… in the treatment of DSPS.”84

Exogenous Melatonin as a Phase-Shifting Agent

Recently, mounting evidence has been reported that exogenous melatonin administration exerts phase-shifting properties (e.g.,85), though some think it may be weaker than properly timed artificial-light exposure.86 Melatonin could be used repeatedly over many days as a strategic countermeasure, slowly leading to a circadian phase advance.85,87,88 There are many recent reviews of the role of endogenous melatonin in sleep regulation and the potential utility of exogenous melatonin for treating sleep disorders (e.g.,89-91).

In an early trial,92 5 mg of melatonin was given at 10:00 PM, 5 hours earlier than the group mean sleep-onset time of the 8 DSPS subjects. The authors reported that the “sleep phase advance occurred within 1-2 days after melatonin was started, and phase delay occurred 1-2 days after the drug was stopped.” Although the data supporting these time frames were not presented in the publication, such an observation also fits within a hypnotic mode of action for melatonin. If it were used as a phase-shifting agent, the phase-advance nighttime sleep-onset time of only 82 minutes after 4 weeks of treatment was far too small to be of significant clinical benefit in this patient population. Interestingly, this protocol of administration of 5 mg of melatonin at 10:00 PM was repeated for 6 weeks in a larger group of 61 DSPS patients.93 At 1-year posttreatment follow-up, 59 of 61 patients self-reported that this 6-week treatment had helped their condition but did not cause a morning hangover as had occurred in the earlier study; 21 subjects reported morning fatigue in this study. The vast majority (92%) of subjects reported relapse by the 1-year follow-up, with 29% experiencing it within 1 week of completing melatonin treatment. In contrast to these data, much lower responding rates have been reported by others with a 3-month administration protocol.

In a variation of this protocol, 5 mg of melatonin was administered 5 hours prior to individually measured dim-light melatonin onset in 25 DSPS patients for a 2-week period.95 On average, dim-light melatonin onset was reported to have advanced by 98 minutes. However, there was not a significant difference in core body temperature, and the protocol allowed sleep to occur during the “semi-constant routine,” and, hence, estimations of the temperature nadir are highly suspect.96,97 Curiously, although there was minimal effect of exogenous melatonin treatment on sleep, as estimated by wrist actigraphy, the authors suggested that their sleep results supported an effect of melatonin as an hypnotic and not as a phase-shifting agent.

In summary, the results of studies of exogenous melatonin to advance circadian phase in DSPS patients have methodologic flaws and show limited and variable results.

Exogenous Melatonin as an Hypnotic

There is also evidence that exogenous melatonin may act as a hypnotic but only when given at circadian phases when endogenous melatonin is at low levels.98,99 Melatonin could be used in a tactical manner, as a circadian phase-dependent hypnotic to gain a faster sleep onset when desired bedtime occurs during the wake-maintenance zone.99 Interestingly, it is possible that by directly suppressing the wake-promoting signal of the pacemaker and allowing sleep onset at this earlier hour, exogenous melatonin might also achieve an indirect positive effect on DSPS, via blocking light exposure during the phase-delay region of the light PRC due to eyelid closure and room lights being turned off for sleeping, thereby leading to a gradual phase advance independent of the putative phase-shifting property of exogenous melatonin. In studies attempting to use melatonin as a phase-shifting agent, this circadian phase-dependent hypnotic mode of action has been acknowledged as an alternative hypothesis for findings (e.g.,95).

Posttreatment Recommendations

Regardless of treatment modality, there are standard steps required to ensure maintenance of the new schedule and to reduce the likelihood of immediate return of symptoms. After the patient reaches the goal bedtime and hence rising time, the behavioral prescription is adjusted. First and foremost, the need for rigid adherence to the new sleep schedule, 7 days a week, is impressed upon the patient.41 Lighting should be dim for at least several hours prior to bedtime to avoid inadvertent phase delay from even average indoor lighting levels and should be as bright as possible upon wake time. This change in lighting may help to stabilize the circadian system at the new phase angle with the light-dark cycle and the desired sleep schedule, preventing inadvertent phase delay. As with all long-term behavior change, there is a cognitive component that should not be underestimated. The clinician must recognize any cognitive distortions made by the patient and act to assist in challenging them. Accurate data collection from the pretreatment and treatment sleep diaries can be instrumental in challenging such distortions (e.g., overgeneralizations about sleep latency, catastrophization about next-day consequences of reduced total sleep time). Finally, napping should be discouraged. Daytime napping will decrease sleep homeostatic pressure and delay nighttime sleep onset and may lead to a recurrence of symptoms.

Other Treatment Considerations

In terms of financial cost, phototherapy is perhaps the most expensive option available. A light bulb must be purchased or rented by the patient. Light visors or light boxes typically cost in the range of $200 to $400, versus much less for a month-long
supply of melatonin. However, the possible recurrence of the DSPS symptoms after treatment and hence the need for periodic re-treatment may require additional melatonin purchases, making a light box and melatonin closer to equivalent in cost over the long run. In terms of economic cost, there is the highest opportunity cost associated with chronotherapy. To follow the prescription of chronotherapy requires a week or more of time off from work or school. Thus, the cost of lost wages and/or wasted educational expenditure may far outweigh the cost of a light box. Among many unanswered questions are the relative efficacy and the effectiveness of chronotherapy, phototherapy, and exogenous melatonin in the treatment of DSPS. Further, it remains a possibility that treatment matching may be possible; particular patients may respond better to 1 modality than another. Alternatively, as with many medical or psychiatric disorders, combination treatments have been proposed and reported,100 but the lack of randomized controlled trials limits comment. Finally, future research may find a role for properly timed exercise101 as a primary or adjunctive treatment for DSPS.

FUTURE CONSIDERATIONS

If future basic work in this area solidifies a biologic or genetic basis for the disorder, then the public and healthcare professionals must be made aware. To do otherwise would be to risk continued misperception of patients simply being “lazy,” unmotivated, or eccentric in choosing to live on a schedule incompatible with that of much of diurnal society. Recognition of the relatively widespread prevalence of DSPS should add fodder to the discussion of school start times, which ironically start earliest for those most likely to be affected by the disorder. Future research should clarify if DSPS represents the endpoint of the morningness-to-eveningness distribution, such as is assessed using the “Owl & Lark” questionnaire102 or a discontinuity from the normal-to-eveningness distribution, such as is assessed using the “Owl & Lark” questionnaire. Future research must be made aware. To do otherwise would be to risk continued misperception of patients simply being “lazy,” unmotivated, or eccentric in choosing to live on a schedule incompatible with that of much of diurnal society. Recognition of the relatively widespread prevalence of DSPS should add fodder to the discussion of school start times, which ironically start earliest for those most likely to be affected by the disorder. Alternatively, as with many medical or psychiatric disorders, combination treatments have been proposed and reported,100 but the lack of randomized controlled trials limits comment. Finally, future research may find a role for properly timed exercise101 as a primary or adjunctive treatment for DSPS.

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