

Delayed sleep-wake phase disorder

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Abstract: Delayed sleep-wake phase disorder (DSWPD) is the most commonly encountered of the circadian rhythm sleep-wake disorders (CRSDs), and is often confused with sleep initiation insomnia. It typically emerges in teenage years and persists into adulthood. In essence, people with the disorder have an abnormally delayed major sleep episode relative to the dark phase of the solar cycle, and hence great difficulty initiating sleep at an appropriately early time, and, as a knock-on effect, waking at a desirable time in the morning, leading to chronic, and often quite severe sleep restriction trying to conform to a 9 to 5 schedule. As a result, sleep on free days is often extended in compensation. When released from such schedule constraints, sleep duration and quality is normal; it is just delayed. This review highlights elements of our current understanding of the epidemiology, associations and pathophysiology of the disorder, before discussing how some of our knowledge of sleep and circadian physiology can be applied to guide treatment of it.

Keywords: Sleep wake disorders; circadian rhythm; melatonin

Submitted Nov 22, 2017. Accepted for publication Nov 27, 2017.

doi: 10.21037/jtd.2018.01.11

View this article at: <http://dx.doi.org/10.21037/jtd.2018.01.11>

Introduction

Delayed sleep-wake phase disorder (DSWPD) (1) is thought to be the most common of the circadian rhythm sleep-wake disorders (CRSDs); an increasingly recognized and diagnosed group of sleep disorders in which the main problem is inappropriate timing of the major sleep episode relative to the light-dark cycle. Their names are self-explanatory, and as well as DSWPD include Advanced Sleep Wake Phase Disorder, in which the major sleep episode occurs every 24 h, but inappropriately early relative to darkness; the non-24 h Sleep-Wake Phase Disorder, in which the major sleep episode is desynchronised from the light-dark cycle, and assumes its own period of greater than 24 h; and irregular sleep-wake disorder, where there is no temporal pattern to the major sleep episode. These disorders may be considered 'intrinsic', and are often chronic, and caused by a variety of factors. On the other hand, 'extrinsic' CRSDs also occur, and are caused by imposition of a different light-dark cycle (as in Jet Lag

Disorder) or routine (Shift-Work Disorder).

The control of timing of the major sleep episode is complex, and dependent largely on synchronised timing of two factors: circadian processes, and sleep homeostatic processes. When aligned, these generate a regular pattern of sleep and wake, whereby sleep broadly coincides with the solar night, and wake with the solar day, which can be mathematically predicted [the Two Process Model of sleep wake regulation—for a review and appraisal see (2)]. This mathematical relationship has been taken further to explain some of the pathophysiological principles of CRSDs (3). In true DSWPD, both circadian and sleep timing are delayed relative to the solar cycle. However, a high proportion of people with the disorder will just have a delayed sleep episode, with normally aligned and entrained circadian timing. The resulting abnormal entrainment and chronic sleep restriction are thought to contribute to numerous deleterious physical and mental health effects, the impact of which are only just beginning to become more appreciated.

This review gives a broad clinical overview of the

disorder, assuming a basic level of understanding of the properties of circadian rhythms and sleep-wake control. Many introductory chapters and reviews have been written outlining the physiology relevant to CRSDs (4-9), as well as several manuscripts providing broad overviews of the circadian rhythm sleep disorders in a clinical context (10-13).

Epidemiology

The true prevalence of DSWPD is difficult to estimate, not least due to issues of definition, differing diagnostic criteria and assessment methods, but also knowing where the boundary between individuals with an extreme evening chronotype and DSWPD exists, and also whether or not prevalence differs as a function of geographical location or socioeconomic factors.

From the available literature, prevalence estimates of the disorder in adults, from studies utilizing large scale, population-based surveying methods (generally a postal screen with subsequent interview), and recognized diagnostic criteria, are around the 1% mark; with an earlier Norwegian study deriving a prevalence of 0.17% (14), and a more recent study from New Zealand, with a similar initial sample size to the Norwegian study, noting a greater prevalence of 1.51% (15). The latter study also found an 8.90% prevalence of moderate to extreme evening chronotypes (as assessed using the Munich Chronotyping Questionnaire) amongst the study cohort (15).

The disorder is felt to be most prevalent in teenagers. Another Norwegian population-based prevalence study, again using recognized diagnostic criteria, similarly powered to the adult studies described above, found a prevalence of 3.3% in teenagers (3.7% in females, 2.7% in males) (16). However, over half of the respondents meeting the diagnostic criteria for DSWPD also met those for used in this study for insomnia (16). Two smaller studies, one from Norway, and one from Australia, derived prevalences of 8.4% (17) and 1.1% (18) respectively, but the latter study noted that over half of the individuals met at least one of the diagnostic criterion for DSWPD, which highlights a common problem with these studies.

In an attempt to bridge the gap in knowledge and provide a unified prevalence for both adolescents and young adults (ages 16–26), as well as establish the prevalence of merely evening chronotype versus DSWPD, a recent small Swedish study found a DSWPD prevalence of 4.6% in this age group (compared to a prevalence of just delayed sleep phase without the full disorder of 4.0%) (19).

Another factor in need of consideration is that these prevalence studies cannot differentiate between ‘circadian’ and ‘non-circadian’ DSWPD. A recent Australian study from a clinic-based sample of 182 DSWPD patients found that only 57% had a true phase-delay (as measured by a delayed salivary dim light melatonin onset (DLMO) time occurring at or after desired bedtime), and as such, were designated true ‘circadian’ DSWPD, whereas 43% (DLMO occurring at or before desired bedtime) were designated ‘non-circadian’ (20).

Associations

Criterion E of the ICSD3 diagnostic criteria for DSWPD gives little flexibility to consider the disorder as anything other than a primary, intrinsic sleep disorder (1). In its purest form, circadian (or primary) DSWPD, which this review goes on to make mechanistic and treatment assumptions about, probably is just that. However, in sleep medicine practice, causality questions often exist: Is the presenting complaint of an unacceptably delayed phase of sleep onset a manifestation of an underlying neurodevelopmental, neuropsychiatric or psychiatric disorder (i.e., ‘secondary’ DSWPD)?

Many patients with DSWPD will have co-existent mental health concerns. Indeed, one small series of patients with DSWPD or extreme evening chronotype found as many as 70% to have a diagnosable axis 1 psychiatric disorder (21).

Affective disorders can manifest with a wide variety of sleep disturbances, and it can be difficult to tease apart and characterise these. Within these disturbances, a tendency towards phase delay is described, and may be more marked in younger patients with depression, than older. Relevant studies have found that 64% of 90 adults with moderate to severe depression meet the criteria for DSWPD (22); and another demonstrated delayed sleep timing in 18% of 305 depressed teenagers, compared to only 10% of matched controls (23). A small cohort series of patients with bipolar disorder found that 62% also met the diagnostic criteria for DSWPD (24).

Of interest, it would seem that patients with true ‘circadian’ DSWPD (delayed timing of melatonin secretion) are more prone to depression than those with non-circadian DSWPD (20). A study from South Korea suggested seasonal affective disorder was 3.3 times more common amongst patients with DSWPD than controls (25). Both of these studies would seem to suggest strong chronobiological influences.

There also appears to be a fairly robust co-association between DSWPD and obsessive-compulsive disorder (26,27). Other well-known co-associations exist between DSWPD and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) (28) and autistic spectrum disorder (ASD) (29). Small case series of individuals with both DSWPD and ADHD have demonstrated disruptions in skin and core body temperature, but not melatonin, rhythms (30), and others have correlated the magnitude of delay with severity of ADHD (31). Furthermore, a recent pilot study used morning bright light therapy to phase advance patients with ADHD, leading to an overall improvement in ADHD symptoms, as well as in sleep and circadian measures (32). Patients with ASD have a high incidence of sleep disorders, including circadian rhythm sleep wake disorders, of which DSWPD is the most common phenotype (29).

In addition to the disorders listed above, a recent piece of work has highlighted a significant phase delay in patients with cystic fibrosis compared to controls; a delay shown to be independent of disease characteristics predictive of survival, which the study authors took to suggest that sleep phase delay is a primary manifestation of CFTR dysfunction in the central nervous system (33).

Pathophysiology

Numerous factors are likely to contribute to the pathophysiology of DSWPS, including behavioural and psychological, as well as biological factors. In terms of the latter, individual differences in neural responses to light, genetics and sleep homeostasis are likely to be of importance.

Light is the most important time cue (*Zeitgeber*) which entrains sleep-wake timing to the solar cycle, via the short-wavelength blue component of the white light spectrum. Light intensity is sensed by the melanopsin containing intrinsically photosensitive retinal ganglion cells in the eye, and conveyed to the central pacemaker, the suprachiasmatic nucleus, via the retinohypothalamic tract (8). At the core of the pathophysiology of DSWPD is the likely scenario that patients receive too much light exposure in the phase delaying portion of their phase response curve to light, and too little, or none, in the phase advancing portion, by virtue of the fact they are asleep. This then generates self-perpetuating 'mal' entrainment: the period length of the sleep-wake cycle approximates that of the solar cycle (24 h), but its phase is inappropriately delayed relative to it.

The importance of evening artificial light exposure as a phase delaying mechanism cannot be underestimated. Studies in healthy volunteers have sought to quantify the melatonin-suppressing, phase-delaying and sleep-modifying effects of standard polychromatic compositions of indoor lighting typically used in evening hours between dusk and bedtime in a controlled laboratory setting (34,35). This has also been demonstrated in naturalistic experiments, whereby subjects lived under their normal conditions, and then were restudied in the wilderness with just solar light, showing quickly changing (advancing) phase angles under these different conditions; the greatest changes being demonstrated as those who were constitutionally more of an evening chronotype (36). More recent extension studies show that this change can happen rapidly, in as little as 2 days, or a weekend (37). Phase delays have also been demonstrated in people living in urban as opposed to rural environments (without electricity) in a similar geographical location in the developing world (38). These effects appear to show high levels of reproducibility within individuals, suggesting that there may be an ophthalmic phenotype in late chronotypes or patients with DSWPD which makes them more sensitive to the phase delaying effects of evening light (39). The melanopsin photoreceptor system is also involved in pupillary light responses, and one study has correlated chronotype to certain facets of pupillary function, which may form the basis of an assay to further tease out these physiological traits (40). Converse to evening light, patients with DSWPD may not be benefitting from the phase advancing effects of morning light (at their most efficacious in the hours following the core body temperature minimum), as they may sleep through this, and as such, the more powerful, less opposed phase delaying effect of evening light is the dominant *Zeitgeber*.

It has also been postulated that the intrinsic circadian period (or tau) of patients with DSWPD, which are determined by the temporal course of the molecular feedback loops within neurons of the suprachiasmatic nucleus (8), may be modestly longer than that of normal chronotypes (which is on average 24.17 h). Some evidence for this exists in evening chronotypes (41), as well as patients with DSWPD taking part in forced desynchrony protocols in which the sleep wake cycle is scheduled to period lengths to which the pacemaker cannot entrain (and hence it 'free runs') (42). It has been suggested in studies of normal volunteers that the free running period length of melatonin of an individual could be correlated to the period length of the same individual's cultured *in vitro* fibroblast

rhythm, whereby the fibroblasts had been modified to express firefly luciferase driven by the promoter of the clock gene *BMAL1* and hence engineered to emit a measurable, circadian light signal (43). No significant difference in fibroblast period length was demonstrated in a recent study comparing cultures from DSWPD patients and controls, although a greater period length was seen in a separate group of normally sighted patients studied how had the related circadian rhythm sleep wake disorder, the non-24 h sleep-wake disorder (or 'free-running' disorder) (44).

The field of chronobiology was greatly accelerated by study of families with another CRSD, familial advanced sleep wake phase disorder, which uncovered mutations in a number of genes found to play significant canonical roles within the suprachiasmatic nucleus. Until very recently, no such genetic mutation had been found for DSWPD. However, a recent study of unrelated families showing strong heritability of DSWPD elucidated a gain of function mutation in the *CRY1* clock gene, which creates a transcriptional inhibitor with enhanced affinity for circadian activator proteins Clock and Bmal1. This allele is found in 0.6% of the population, and may play a significant role in delayed sleep timing (45).

Prior to this discovery, attention had largely focused on another of the clock genes: *PER3*. Five polymorphisms are known; including a variable number tandem repeat (VNTR) of either 4 or 5 repeated motifs. The homozygous 4-repeat allele (*PER3*^{4/4}) was found more frequently in UK patients with DSWPD (46), but was however inversely related to DSWPD in a replication study in Brazil (47), which the authors argued might be explained by latitudinal differences, and argues against any absolute association. Perhaps of greater overall importance, individuals who are homozygous *PER3*^{5/5} may have advanced melatonin rhythms (48), which may actually be protective against significant phase delay tendencies. If this is the case, then somewhat puzzlingly, *PER3*^{5/5} individuals demonstrated greater melatonin suppression from blue light in the evening compared to those who are *PER3*^{4/4} (49), however, this is likely to be offset by a stronger, earlier chronotype conveyed by this polymorphism, in addition to the possibility of enhanced sensitivity to the phase advancing effects of morning light.

A further mechanism contributing to the development of DSWPD is likely to be intrinsic differences in sleep homeostasis in individuals who develop the disorder. Slow wave sleep precipitously falls in mid puberty (50), a critical window during which DSWPD symptoms can emerge, which could give credence to the theory that alterations in sleep homeostasis could precipitate

development of the disorder (51). Quantitative analysis of sleep electroencephalography (EEG) has suggested that slow wave activity, the best marker of the sleep homeostatic mechanism (restorative response to sleep deprivation) of an individual, decreases with less magnitude in the first sleep cycle in evening chronotypes compared to normal or intermediate chronotypes (52,53), despite no real differences in baseline sleep being noted between patients with DSWPD and controls (54). This study also demonstrated a normal phase angle relationship between sleep onset and the rise of melatonin, which contrasts to earlier work suggesting a correlation between evening types and shorter phase angles (55). Attempts to mathematically model the relative influences of sleep homeostasis and the circadian pacemaker on chronotype have further explored these interactions (56). Functional imaging techniques have been used to study individuals of extreme chronotype (both morning and evening), and differentially demonstrated greater activity in the suprachiasmatic nucleus (pacemaker) and locus coeruleus in the evening hours in evening types compared to morning types (57). Animal work has suggested that the locus coeruleus is thought directly involved in the sleep homeostatic response via its noradrenergic projections (58).

Assessment

Clinical assessment involves eliciting an enduring history of difficulty both falling asleep and waking at socially appropriate times, but otherwise normal sleep when left to sleep ad libitum. Remembering these fundamental features of DSWPD is helpful in differentiating it from sleep initiation insomnia. For the diagnosis to stand, other sleep disorders need to be absent (or treated). Furthermore, a comprehensive assessment should also include an account of past and current mental health, particularly given the co-associations described above. Formal psychiatric evaluation may be of use in patients in whom these disorders may exist, or are known to exist and are inadequately treated.

Longitudinal wrist actigraphy with contemporaneous sleep diaries is the most useful, and recommended (59), assessment tool, and the data generated from these should be used to calculate various mean phase markers on 'free days' (i.e., days with no social or work commitments). In practice, this will often mean needing to capture data across three consecutive weekends. Of the sleep phase markers, the mean midpoint of sleep on free days (sleep immediately preceding days without time-dependent commitments) appears to correlate most strongly to the 'gold standard'

laboratory-derived melatonin phase markers (60), although re-analysis of pre-existing data has suggested that some consideration to midpoint of sleep on work days should also be given (61).

A commonly used laboratory-derived phase marker is salivary DLMO time, or DLMO, which relatively speaking is also the most straight forward to ascertain. However, the drawback of this technique is that it does not provide an immediate phase marker, as the samples need to be processed and assayed, the collection technique is subject to a variety of confounders and is costly to perform. Wearable technology also suggests that wrist skin temperature may track DLMO with reasonable accuracy as well, and maybe a technique worthy of further development and trials (62).

An analysis of peripheral white blood cell transcriptome data has also concluded that collection of two samples, 180 circadian degrees (12 h) apart, may also accurately estimate phase (63). This technique may have interesting clinical applications, but would also be subject to the same time lag from collection to result as melatonin currently is. It may have considerable utility in assessing treatment response.

Therapy

A multifactorial approach is needed for the treatment of DSWPD, which addresses initial phase advancement (initiation), subsequent phase retention (maintenance), and due consideration of other disorders which may be associated with, or exacerbating, the problem, most notably ADHD, ASD, affective disorders and obsessive compulsive disorder (OCD). It is important to establish a balance between an ideal and realistic sleep onset and offset time with patients, to manage expectation, and spend quite some time explaining the rationale and steps of treatment.

Large-scale randomised-controlled trials in patient populations are lacking, and therefore little clinical evidence exists to guide best practice management of the disorder. This dearth of useable evidence has been highlighted in a recent update to the American Academy of Sleep Medicine Task Force statement on CRSD treatment; a systematic review of available studies which at best was able to grade the evidence for strategically timed melatonin alone as treatment for DSWPD in children and adolescents as being “moderate” in quality (64). However, despite the lack of clinical evidence, the application of well-described scientific data to the clinical problem, based on some of the pathophysiological principles outlined above, seems a logical and helpful foundation to start from.

While Melatonin is the traditional mainstay, and perhaps best described, treatment for DSWPD, its use is seldom systematically prescribed or adhered to. In the UK and EU, Melatonin is a prescription-only medication, used largely ‘off label’ as an unlicensed treatment for DSWPD, whereas in other countries, most notably the USA, it is considered a supplement, and freely available off-the-shelf. Currently, in the UK at least, the main preparation of Melatonin is a controlled-release 2 mg tablet. Other preparations, such as 3 mg tablets of immediate-release Melatonin, or specially manufactured liquid Melatonin, are typically only available through specialist centres and pharmacies. Melatonin is generally very well tolerated with few side-effects, although given lack of data, rather than safety concerns, its use is avoided in pregnancy and breastfeeding. Those most frequently reported include headache and nasopharyngitis. Caution should be used in patients with hepatic impairment. There are few interactions, although some CYP1A effects may be seen (Rifampicin, Carbamazepine, Quinolones and smoking may reduce levels; certain oestrogens may increase levels). Endogenous melatonin levels are said to be reduced by concomitant use of beta blockers and non-steroidal anti-inflammatory drugs. No trial has ever documented any serious adverse effect from use of Melatonin, and two observational long-term use studies in children and adolescents (median follow-up 4 years) have not documented any safety concerns (65,66).

Scientific evidence suggests use of strategically timed 0.5 mg daily doses of Melatonin is as effective, and potentially less sedating than larger doses at affecting phase shifts (67). As such, it is often worth explaining to patients that the effect is not designed to be hypnotic, rather it is designed to act as a time cue. Phase response curves ascertained in detailed laboratory studies in healthy volunteers are also available for this dose (67). They estimate that for the greatest magnitude of phase-advance to occur, 0.5 mg Melatonin should be taken approximately 10–12 hours prior to the mean mid-point of sleep on free days (or 6–8 hours prior to the mean sleep onset time on free days). As consistency is key, patients should set alarms to remind them to take the melatonin. When taken correctly and consistently, this can affect a 90-minute (+/- 30 minute) phase advance. Thereafter, once a new steady-state phase has been achieved (reassessed after a week or two), the mid-point of sleep on free days can be recalculated, and the dosing time bought forward again. In practice, up to three step-wise advances might be necessary. A 0.5 mg dose of Melatonin can be achieved by quartering

a 2 mg prolonged-release Melatonin tablet (68). This will sufficiently disrupt the coating to render the preparation immediate-release.

As well as appropriately dosed and timed Melatonin, equal importance should be paid to the phase-delaying and Melatonin suppressing effects of evening light in individuals with DSWPD. In a few patients, a significant phase advance may be bought about by just minimizing exposure to evening (artificial, indoor) light, from dusk, and analogies can be made in clinic to the camping experiments described above (36-38). In practice however, an effective way of doing this, in addition to minimizing or dimming indoor lighting, may be the use of blue-light filtering goggles or glasses with amber lenses (69). Patients are instructed to wear these from sunset until bedtime.

While avoiding the more potent phase-shifting (delaying) effect of evening light is arguably the more important light paradigm, timed morning light (phase-advancing) exposure is highly beneficial. Morning light exposure is likely to be most helpful in phase-advancing, or promoting an additive phase-advancing effect together with Melatonin and evening light avoidance, if it is delivered as soon as possible (preferably immediately) after waking. The best method for this is natural light, and patients should be encouraged to get outside into daylight as quickly as possible after waking, for 30 minutes. Where not possible, sitting next to a well-lit window can be effective. In winter months, or those patients with no access to outdoor light, bright artificial light therapy can be used, and there are a variety of light boxes available for this purpose. Scientific studies have used a variety of light intensity and duration paradigms. The best studied is that of 10,000 lux bright light delivered for approximately 30 minutes on waking. Due attention needs to be paid to the distance the light box should be from the patient, with most requiring a distance of 30–50 cm to deliver this intensity. Larger devices may deliver 10,000 lux up to 85 cm away. Many patients will find this quite cumbersome, restrictive and uncomfortable to use, so ‘wearable’ light devices, in the form of LED-light emitting spectacles, have been designed, but no clear evidence of efficacy currently exists.

Combination therapy with timed lighting paradigms, utilizing both phase-advance reinforcing light exposures (filtering evening light with orange goggles or enhancing morning light with goggles fitted with blue light emitting light emitting diodes) or phase-delaying light exposures (the reverse) and advancing sleep times, demonstrate greater phase shift magnitudes than either method alone (70), and

this has also been replicated to some extent in similar studies in people with clinical (71) or subclinical DSWPD (72).

Treatment of co-morbid insomnia is also very important, and patients may well benefit from a course of cognitive behavioural therapy for insomnia once a target phase advance has been approximated (73). This may be particularly helpful in terms of phase-maintenance. DSWPD focused cognitive behavioural therapy (CBT) is also being developed, and indeed a tailored approach combining aspects of both CBT for insomnia, CBT for DSWPD and general sleep and circadian psychoeducation (‘chrono-education’) is likely to be the optimum behavioural adjunct for treatment (74).

Although chronotherapy is used in children and some adults, particularly those with very profound phase delays, this would generally be reserved for patients in whom a satisfactory phase advance could not be achieved with the above measures, and delivered only by sleep therapists with experience in this technique, as it runs the risk of causing desynchronization to a non-24 h sleep-wake disorder.

Relapses in treatment and decompensation are common, and patients should be counselled for this eventuality, and encouraged to follow their original treatment plans should this occur.

Conclusions

Delayed sleep wake phase disorder is a relatively common sleep disorder with clear associations and tangible likely pathophysiological mechanisms. Further understanding of this disorder is likely to need to experimentally probe these potential mechanisms further, and use data derived from this pilot work to generate larger scale randomised therapy and prevention trials to help ascertain the best treatment modalities for the disorder.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Nesbitt AD. Delayed sleep-wake phase disorder. *J Thorac Dis* 2018;10(Suppl 1):S103-S111. doi: 10.21037/jtd.2018.01.11