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REVIEW ARTICLE

Updates and confounding factors in delayed sleep–wake phase disorder

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Abstract

Delayed sleep–wake phase disorder (DSWPD) is a circadian rhythm sleep disorder characterised by a delay in the main sleep period, with patients experiencing difficulty getting to sleep and waking up at socially appropriate times. This often causes insomnia and compromised sleep, results in impairment to daytime function and is associated with a range of comorbidities. Besides interventions aimed at ameliorating symptoms, there is good evidence supporting successful phase advancement with bright light therapy or melatonin administration. However, no treatment to date addresses the tendency to phase delay, which is a common factor amongst the various contributing causes of DSWPD. Circadian phase markers such as core body temperature and circulating melatonin typically correlate well with sleep timing in healthy patients, but numerous variations exist in DSWPD patients that can make these unpredictable for use in diagnostics. There is also increasing evidence that, on top of problems with the circadian cycle, sleep homeostatic processes actually differ in DSWPD patients compared to controls. This naturally has ramifications for management but also for the current approach to the pathogenesis itself in which DSWPD is considered a purely circadian disorder. This review collates what is known on the causes and treatments of DSWPD, addresses the pitfalls in diagnosis and discusses the implications of current data on modified sleep homeostasis, making clinical recommendations and directing future research.

Keywords Circadian · Phase · Delay · Homeostasis

Preamble

Delayed sleep–wake phase disorder (DSWPD) is a circadian rhythm sleep disorder characterised by a delay in the main sleep period with patients experiencing difficulty getting to sleep and waking up at socially appropriate times. This is associated with insomnia and/ or daytime sleepiness and results in impairment of daytime function. According to the International Classification of Sleep Disorders (ICSD-3) this delay is recurrent for at least 3 months and is not better explained by another sleep, mental or medical disorder. Furthermore, patients allowed to sleep ad libitum will maintain a delayed sleep phase but experience improved sleep quality and duration.

Besides significant impairment to daytime function [1] this often results in extreme sleep inertia, increased sleep onset latency and poor sleep quality [2]. Attempts to cope with symptoms (e.g. napping and recovery sleep, stimulant or hypnotic use) can in themselves further delay the sleep phase or disrupt sleep [1, 3]. Sleep deprivation causes significant cognitive and functional compromise and is in itself a significant health risk [4]. However, independent of sleep duration, DSWPD and circadian misalignment, in general, are associated with impaired cognitive function [2], adverse metabolic changes [5, 6], increased incidence of a range of psychiatric disturbances [7, 8] and generally compromised quality of life [1, 9].

As with most circadian disorders, understanding of DSWPD remains disparate, particularly with regard to aetiology. This review seeks to provide an up-to-date summary of present knowledge on the causes and treatment of DSWPD, as well as discuss the complexities of diagnosis. Furthermore, in evaluating current findings on sleep homeostasis in DSWPD patients, this review will call into question the purely circadian pathogenesis of DSWPD and emphasise the need to review assumptions on sleep homeostasis in clinical treatment.

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Diagnosis

Assessment of the delayed phase may be made by recording sleep and activity itself, by self-assessment of diurnal preference or by measuring diurnal variations in physiological variables. The latter most often refers to either timing of minimum core body temperature (CTmin) or the evening melatonin surge also known as dim light melatonin onset (DLMO). Behavioural and activity indicators have to be used with care, however, because amongst the comorbidities of DSWPD are some that further confound symptoms. Examples of these are secondary insomnia [10, 11], substance misuse [12], depression [7, 9] and other psychiatric disorders [7, 13].

Self-assessment of evening preference, usually by the Horne and Östberg morningness-eveningness questionnaire [14], is associated with delayed sleep periods [15–17], delayed body temperature rhythms [18] and delayed melatonin rhythms [19]. However, this will have to be considered alongside more direct measures of phase delay, particularly to assess whether the evening preference is sufficient to constitute DSWPD [1].

In healthy individuals sleep diaries can predict DLMO within about an hour [20–23], but this is not the case in patients suffering from insomnia [24] or circadian disorders [25]. In DSWPD patients specifically there seems to be a tendency for a sleep period to be more delayed than a circadian period, compared to controls [9, 26], and in evening types in general there was a weaker association between sleep periods and circadian rhythm [27]. If there is a need to use sleep diaries to assess phase delay, then they should be from days of unrestricted sleep (e.g. weekends and holidays) [23] and can be supported with actigraphy measurements [28].

Delayed DLMO is highly sensitive and specific for DSWPD [29, 30] and is useful for distinguishing DSWPD from conditions that may present similarly but have either an extrinsic circadian or non-circadian cause (e.g. jet lag and primary insomnia, respectively) [29, 31]. However, there can be unpredictable variations in the temporal relationship between DLMO and sleep in circadian disorders [32]. Although the phase relationship between DLMO and sleep onset is similar in DSWPD patients and controls [30, 33, 34], Shibui et al. [30] reported delayed sleep offset relative to DLMO in DPSD patients. Furthermore, DLMO appears to have a different predictive value on sleep propensity in DSWPD patients compared to controls [35]. Despite its diagnostic value, it seems that the relationship of DLMO to sleep variables and certain assumptions regarding the significance of DLMO should be reconsidered in DPSD patients.

Similar constraints exist with CTmin as a metric. Numerous studies have reported differences in the interval between CTmin and both sleep onset and offset in DSWPD patients compared to controls (i.e., in which part of the sleep period CTmin occurs) [9, 11, 35–38]. More generally, CTmin is also easily confounded by factors such as posture, activity and arousal [39] and even in healthy individuals there appears to be interindividual variation in the relationship between CTmin and sleep period [31].

Treatment

Exogenous melatonin administration shifts phase [40, 41] according to a phase response curve roughly inverse to that of light [23, 42] – taken in the early evening prior to DLMO it advances the circadian phase. This is seen as advances in the sleep period (including both onset and offset) [43] as well as in the endogenous melatonin rhythm [44], though not in body temperature rhythm [45]. Patients also show improved sleep and quality of life parameters including reduced sleep onset latency, subjective sleep improvement [46] and reduced daytime sleepiness [47].

Timing of administration affects the magnitude of phase shift [41] but dose variation does not [41, 48], although different doses may have different optimum timings for a maximum phase shift [49]. High and low doses also give very similar improvements in sleep parameters [50]. Mundey [41] recommends individual phase response curves should be measured prior to melatonin administration (see the section on variations), where DLMO is a particularly significant landmark around which administration should be planned [51]. Exogenous melatonin administration is the recommended treatment for DSWPD under the 2015 American Academy of Sleep Medicine guidelines [52] and various examples of treatment protocols have been described [42, 48, 53]. Patients are widely reported to relapse after treatment, however, [41, 43, 46], and the timing of relapse seems associated with the severity of phase delay prior to treatment [46].

Light alone is a sufficient zeitgeber for clock entrainment [54]. Morning exposure to bright light (i.e. shortly after CTmin) advances the circadian phase and sleep period according to a phase response curve [55–59]. These results have been replicated in patients with circadian rhythm disorders, including DSWPD. In DSWPD patients morning bright light therapy advanced the circadian phase as measured by DLMO [60] and CTmin [61], also consistently advancing the sleep period, however changes in sleep parameters have been very mixed [52, 62, 63]. Yamadera et al. [64] found it improved sleep quality and reduced daytime sleepiness and Cole et al. [65] also found it improved sleep quality but not morning sleepiness or total sleep time. Rosenthal et al. [61] and Faulkner et al. [63] both reported improved sleep onset latency, however, the latter found no significant

improvement in sleep quality, daytime sleepiness or total sleep time and only a mild improvement in sleep efficiency.

Besides timing, intensity and duration of light treatment affect the magnitude of phase shift and change in sleep parameters [57, 61, 66], however, optimal dose and duration have yet to be determined [67]. It is generally recommended that individual phase response curves to light be assessed prior to treatment [55, 56, 59, 68] (see discussion on variations elsewhere in the text). Maximal effect is seen in the blue light spectrum (420–500 nm) [69–72], and using lower-intensity white light for longer periods may prove more effective [73]. If side effects such as headaches are encountered light intensity and duration can be decreased but the length of treatment increased instead [74, 75]. Compliance can be poor [41] and even where achieved symptom relapse is still deemed likely [1, 76] and 'booster administrations' may be needed [75]. Inpatient delivery has shown high response rates, suggesting the importance of compliance, but even in these cases the rate of symptom relapse following discharge has been high. [77, 78]

Bright light therapy and melatonin administration do not contraindicate each other, and it has been hypothesised that their effects may be synergistic [79]. Various studies have found combination therapy of light and melatonin to produce greater phase advance in healthy patients than either therapy alone, although results appear to be additive rather than synergistic [80–82]. A case series by Samaranayake et al. has confirmed this finding in DSWPD patients [83]. Surprisingly, though, a randomised clinical trial in a DSWPD population showed patients treated with both melatonin and bright light had no significant difference in phase shift or sleep parameters compared to patients receiving either or neither treatment [66, 84].

Hypnotic agents such as benzodiazepines, benzodiazepine receptor antagonists and some antihistamines, amongst others, may be used to promote and maintain sleep. However, this can be associated with reduced sleep quality, daytime sleepiness or cognitive impairment and other adverse effects [85]. More importantly, although hypnotics can advance sleep onset, studies are lacking on their effect on the circadian phase and sleep homeostasis. This is particularly the case in a DSWPD population in which there are likely to be pre-existing variations in both circadian rhythm and sleep homeostasis. There is little evidence supporting the treatment of DSWPD using hypnotics [13, 52].

Besides melatonin, melatonin receptor antagonists (MRAs) have also been developed and from preclinical studies these present potential for the treatment of sleep and circadian disorders. MRAs have also been clinically shown to decrease SOL [86–89] and shift the circadian phase [90–92]. However this is largely in healthy populations and therapeutic use in DSWPD has yet to be demonstrated save for two recent successful case reports using ramelteon [93, 94]. Of these, Shimura et al. in particular [94] suggest that ramelteon should be administered at very low doses for DSWPD. It also remains to be seen how MRAs will compare with melatonin in clinical use.

Suvorexant, an orexin receptor antagonist (ORA), has been shown to improve SOL and sleep maintenance while maintaining normal sleep architecture [95–97], and is approved for the treatment of insomnia in Japan and the United States of America. Treatment resulted in phase advance in two cases [98], and three patients who did not respond to ramelteon as monotherapy responded when suvorexant was added [99]. The mechanism of action of ORAs suggests that it could be useful in DSWPD, at least to advance sleep onset in phase-shifting protocols. Unfortunately, few studies have investigated this.

Another drug that may be promising is aripiprazole which, being a partial agonist of dopamine and serotonin, is believed to influence coordination of these neurotransmitters with melatonin, as well as increase wakefulness by increasing histamine secretion [100, 101]. This has proven effective for DSWPD in several cases [101–103], resulting in phase advance, decreased total sleep time and increased daytime wakefulness, however, there is currently still little evidence supporting aripiprazole therapy.

Improving sleep hygiene does not constitute therapy for DSWPD, much less monotherapy. Whilst aspects of this may improve sleep parameters in healthy patients, those with circadian disorders can have altered sleep homeostatic processes (see elsewhere in the text). For instance in DSWPD patients sleep pressure builds more slowly, and sleep deprivation tends not to advance the sleep phase. Variations in circadian processes, such as altered phase response curves, can also mean DSWPD patients do not respond to sleep hygiene measures as healthy patients do. The bidirectional relationship between sleep homeostasis and clock function (see elsewhere in the text) further undermines assumptions that the benefits of sleep hygiene will apply to DSWPD patients. Most importantly, even if sleep hygiene measures improve sleep in DSWPD patients there is no evidence they can shift the circadian phase, or ameliorate the physiological ill effects of circadian misalignment.

Cognitive behavioural therapy has been described as an adjunct to light therapy for DSWPD, to good effect [104, 105]. It may be useful to maintain desired effects of a successful phase shift, as well as to treat comorbidities of DSWPD that may exacerbate its sequelae, such as substance abuse, insomnia or impaired daytime function. [75, 104]. However, no evidence exists in support of it as sole therapy.

Czeisler et al. [106] described implementing progressive phase delays until the intrinsic rhythm adequately matched zeitgeber time. This was intended to take advantage of DSWPD patients' long-running clocks and tendency to phase delay. Furthermore, patients with more extreme delays

may need many hours' advance to reach a desired bedtime such that delaying may be quicker [75]. Chronotherapy has also been shown to reduce period length [36], which in turn reduces the tendency to phase delay. However, progressive delays may end up risking light exposure at unfavourable times in the PRC [75], and relapse is likely [76, 107]. There have been no randomised clinical trials to date and case studies have given mixed results [13].

Causes

Genetic influence on circadian phenotype in humans has been demonstrated with twin studies [108] and pedigrees [109], and up to 50% of the variance in circadian phenotype has been shown to be heritable [110]. In particular, a 54-base pair long variable number tandem repeat polymorphism on the human period 3 gene (*hPer3*) has been associated with diurnal preference, where the shorter allele correlates strongly with eveningness and DSWPD [111, 112].

A single nucleotide polymorphism in the human clock gene (*hClock*) has also been demonstrated to correlate with diurnal preference, though not specifically with DSWPD [113]. Subsequent mutation screening of *hClock* in DSWPD and control subjects also suggests variations here are unlikely to be associated with DSWPD [114].

There is growing evidence that a long period (tau) is implicated in DSWPD. In other taxa, mutations altering circadian phenotypes generally do so by changing tau length [113]. In humans numerous clinical studies have associated long periods with a phase delay, both in body temperature [11, 36, 115] and melatonin [116] rhythms. A longer period means a constant tendency for phase delay relative to zeitgeber time, which was described early on by Czeisler et al. [106]. However, age-related changes in both melatonin and CT rhythms cannot be accounted for by changes in period length alone [117, 118] and it remains to be investigated whether longer periods can account for the delays observed in DSWPD.

Another suggestion from Czeisler et al. [106] is that DSWPD patients have an altered PRC to light, where the phase advance section is shorter than in controls, thus phase advance is less likely to happen. Evidence for this has generally been lacking [9] but this hypothesis, along with lengthened periods, formed the basis for chronotherapy as described by Czeisler et al. (see elsewhere in the text).

DSWPD patients are more sensitive to the melatonin-suppressing effects of light exposure in the pre-DLMO part of the curve [119, 120], rendering them more prone to phase delay with light exposure. Furthermore, Micic et al. [34] found that, besides being delayed, the melatonin output of DSWPD patients showed a smaller surge than those of controls. The mechanisms have yet to be elucidated.

Lifestyle changes are also purported to cause DSWPD [1], mainly the use of electronic devices with bright display screens. Exposure to light from common electronic devices at relevant portions of the PRC has been shown to cause suppressed melatonin secretion, phase delay, increased SOL and poorer quality sleep [121, 122], increasing the likelihood of a diagnosis of DSWPD. Besides electronic light, evening and morning types have been shown to have different patterns of total light exposure relative to both zeitgeber time and their respective circadian clocks, and the general pattern in evening types tends to lengthen the period [123, 124].

Another crucial lifestyle factor would be the use of stimulants and hypnotics which, on top of altering sleep homeostasis, can cause circadian changes [3, 125]. Individuals already experiencing circadian misalignment or sleep disturbances (e.g. jetlag, insomnia) are more likely to reach for these which may perpetuate existing symptoms [1, 75].

Lack et al. [75] also describe a more psychologically motivated vicious cycle in phase delays. No matter the initiating cause, an individual with a delayed clock will perform more of their daily activities in the evening, including those involving exposure to bright light. They may also wish to prolong this productive period by going to bed later, and when attempting to sleep at conventional times often find themselves unable which only increases anxiety and arousal. On the other hand, waking at conventional times, which may be on or around the time of CTmin, results in adverse sensations of grogginess and discomfort. Avoiding these sensations is a further incentive to sleep through these periods where possible, further contributing to phase delay [126], particularly if they sleep through the phase advance portion of the PRC to light [37].

DSWPD is also highly comorbid with a range of psychiatric disorders [7, 8]. For instance, in borderline personality disorder the prevalence of DSWPD is shown to be significantly higher than in the wider population [127–129]. However, the presence of circadian disorders has also been shown to predict earlier symptom relapse in bipolar disorder [130]. It remains difficult to distinguish which is the cause and which the effect and so psychiatric disorders should be considered a correlation which could be a potential cause.

Sleep homeostasis

Based on Borbely's [131] two-process model, sleep is regulated by the combined effects of a circadian process entrained to the time of day (process C) as well as a homeostatic process responding to sleep pressure (process S). DSWPD and other circadian disorders have been considered to be caused by and to modulate just process C but there is increasing evidence that this may not be the case. Firstly, not just circadian rhythms but also sleep homeostatic mechanisms have been shown to differ in patients with

circadian disorders, suggesting that the causes and results of such disorders may not be purely circadian in origin. More interestingly, even in healthy human subjects and animal models the two processes have been shown to modulate not just each other's output (i.e. sleep regulation) but also their mechanisms [132, 133]. The finer details of this bidirectional relationship and its role in DSWPD aetiology require far more research to evaluate, as does the question of whether the two-process model remains viable in DSWPD.

Circadian clock genes have a role in sleep homeostasis and affect how patients respond to sleep deprivation [132]. Sleep homeostasis in evening types has been shown to differ from that in controls. In evening types sleep pressure builds more slowly than in morning types, as measured by theta wave activity in waking EEGs [134], though eventually reaching similar maxima [135, 136]. Sleep pressure also dissipates more slowly in evening types, with morning types showing more slow wave activity during the initial NREM segment of a sleep period [137].

Data from DSWPD patients in particular show that some sleep variables are significantly different from those in controls. DSWPD patients have decreased total sleep time and sleep efficiency [38], as well as altered distribution of sleep wave patterns and longer SOL even at preferred bedtimes [11]. Sleep homeostatic responses also differ, with DSWPD patients less likely to either have daytime recovery sleep or to advance sleep period following sleep deprivation [138]. Such differences significantly undermine the basis of traditional sleep hygiene practices as therapy for DSWPD.

While evidence of varied sleep homeostasis may often be assumed to be sequelae of DSWPD it also raises the question of whether DSWPD symptoms are the product of, or at least perpetuated by, altered sleep homeostasis. Other authors [34, 138] have suggested that the aetiology of DSWPD may not purely be circadian in origin, and that other physiological processes may be involved in or may even cause the period or sleep delays. Another example of this may be the smaller melatonin peaks observed in DSWPD patients (see elsewhere in the text).

Conversely, circadian processes appear to vary with changes in sleep pressure as well. Many subjective and physiological factors such as cognitive function, mood and EEG activity patterns vary across the circadian day, but the amplitude of this variation has been shown to vary with sleep pressure [139, 140]. Numerous factors that vary with sleep history, such as temperature, cytokine levels and redox state, are likely to contribute to changes in the expression of clock genes [141]. There is also increasing evidence from human and nonhuman studies that variations in the sleep–wake cycle modify entrainment in the suprachiasmatic nucleus where the 'central' clock is [142, 143]. In a murine model, sleep deprivation alters clock gene mRNA levels [144] and also modifies the binding of clock transcription factors to regulatory sequences of target clock genes [145]. It is noteworthy that sleep history can modify circadian processes at the level of gene expression, although human studies are lacking and much more work is required to characterise these effects. This may go some way in explaining 'extrinsic' causes of circadian disorders (e.g. evening electronic device use, travel across time zones) but when considering the 'intrinsic' factors in DSWPD it raises the question of whether genetic expression or sleep disturbance came first.

Recommendations and directions

Treatments for DSWPD should be considered to fall into one of two mechanistic levels. The first seeks to modulate sleep–wake behaviour, typically with the use of stimulants and hypnotics or sleep hygiene strategies, and is something many patients are likely to have attempted in some manner. The other category of treatments aims to shift circadian phase itself so that desired patterns of sleep–wake behaviour and daytime function are a result of cohesive central control rather than simply downstream modification. Some interventions, such as prescribed bedtimes or melatonin administration, can fall into either or both of these categories depending on how they are used.

Whilst the latter category addresses aetiology at its essentially circadian level, relapses are common even where treatment has been successful (see elsewhere in the text). In this author's opinion, there would ideally be a third and yet more fundamental level of intervention, that would correct or adequately circumvent the very tendency to phase delay in the first place. This is currently completely hypothetical and is likely to remain so until much more is known about the pathogenesis. The cause or causes themselves, if found, might not be easily corrected, particularly if genetic in nature. However it is well worth further research to characterise the physiological, neural and molecular mechanisms underlying the aetiology – these comprise a rational target for therapy but are also likely to lend significant insight into other circadian and sleep disorders.

It must be noted that the premise for this whole paper is that DSWPD requires treatment in order for the patient to benefit. Two recent case reports [146] showed improvements in sleep parameters in patients who stopped treatment but were able to change their sleep schedules to suit them due to restrictions during the coronavirus disease 2019 pandemic. This raises the possibility of eliminating circadian mismatch without any treatment at all – the 'intervention' in this case would be modification to social demands placed on patients, which are necessary for the manifestation of pathology. Much more research is needed to characterise this, but benign neglect is an option worth considering if patients can be granted appropriate social accommodations and support.

This paper's discussion of diagnostics reveals numerous complexities in how phase markers and tools of phase assessment relate to sleep variables. In particular, it highlights the need to consider that these may be very different in a population with sleep disorders compared to controls. Despite the practical difficulties associated with DLMO it remains the best-supported diagnostic metric and also the most useful for informing therapy as current knowledge stands. It also allows for quantitative measurement of the magnitude of delay. Once again, a more thorough understanding of the underlying mechanisms would be instrumental. If the relationships between phase measurements and sleep variables can be better predicted then diagnostic processes can be refined accordingly.

What may, in fact, be quite useful in the assessment and management of DSWPD is a way to quantify the severity of the disease, which is currently lacking. The duration of phase delay can easily be measured, but from a clinical perspective it would also be crucial to assess and subsequently track the level of physiological compromise and psychological distress caused to the patient. This could take the form of an index combining a range of sleep variables, particularly considering that these are still difficult to predict in a DSWPD population and considering the sleep homeostatic differences in these patients. Another possibility is a patient questionnaire, which would better capture the qualitative impact of the disorder. This can easily be combined with more objective sleep metrics. The variables to be included and their relative weighting remain to be determined, in both the index and the questionnaire, and the development and validation of these tools lie without the scope of this review.

Numerous genetic and non-genetic factors have been associated with DSWPD, although causation has been established for a few of these. It's unclear which of these factors, if any, are necessary or sufficient conditions for the disorder. There seem to be many possible ways to arrive at the same symptomatology.

This is a disorder that is generally thought of as circadian in both cause and effect, however, it looks as though there are significant differences in sleep homeostasis as well. This is a vital point to consider and certainly a concept warranting much more attention, not least for the chicken-and-egg questions raised but crucially also because the variations in sleep homeostatic processes would likely affect how the disorder can be diagnosed and treated. It is important to question the assumptions that DSWPD patients' sleep homeostatic processes are as expected in healthy patients.

Declarations

Conflict of interest The author declares no conflicts of interest.

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