# Chapter 14
# Circadian Rhythm Sleep-Wake Disorders

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## Introduction

All life forms have intrinsic daily rhythms in cellular activity, physiology, and behavior. These self-sustained biological rhythms are near-24-hour oscillations that allow organisms to coordinate their internal processes to anticipate the environment so that physiological functions occur at the appropriate times. Misalignment of the internal circadian clock with the external 24-hour day-night cycle and/or social behavior can lead to sleep disturbances, daytime impairments, mood disturbances, and increase the risk for chronic disease [1–3].

Circadian properties are determined by both genetic and environmental influences. On a molecular level, circadian rhythms are generated by a transcriptional-translational feedback loop of clock genes and proteins. At its core, the molecular clock consists of a heterodimeric complex of proteins of the genes *CLOCK* and *BMAL1*, which positively regulate the expression of *Period (PER 1,2,3)* and *Cryptochrome* (*CRY 1, 2)* genes which, in turn, form their own transcription repressor complex to inhibit the activity of CLOCK and BMAL1. This feedback loop is further regulated by kinases like casein kinase 1 (CK1) which contribute to timekeeping through the destabilization of PER proteins [4]. The cycle takes

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approximately 24 hours to complete, and disruptions to this molecular system can alter the period and amplitude of circadian rhythms.

On an organismal level, the mammalian circadian system is organized hierarchically. The suprachiasmatic nucleus (SCN) of the hypothalamus is the master clock that not only organizes and synchronizes peripheral clocks to other tissues but also to the 24-hour external environment [5–7]. If humans are isolated from all environmental time cues, their intrinsic circadian rhythms will "free run" with a period slightly longer than 24 hours. In sighted people, the average circadian period is 24.18 hours [8]. Thus, synchronization of the endogenous circadian system to the 24-hour day requires frequent adjustments in response to time cues (zeitgebers) in a process known as entrainment. Light is the most powerful zeitgeber, but a number of external stimuli such as food availability, exercise, social activity, and internal stimuli such as melatonin secretion can also influence this process [9].

Photic information is conveyed from the eyes by melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) that send projections to the SCN via the retinohypothalamic tract [10, 11]. The timing of light exposure is an important aspect of the entrainment process, producing shifts of the circadian rhythm, as demonstrated by the phase response curve (Fig. 14.1). Light exposure in the first half of the night before the nadir of core body temperature will delay circadian timing. Light exposure in the latter half/early morning will advance circadian timing [12]. The magnitude of phase shifting in response to light depends on the time of exposure, intensity, and wavelength as ipRGCs are most sensitive to short-wavelength light [10]. Although light is the strongest signal, non-photic cues can also regulate circadian rhythm timing. Melatonin is a hormone secreted by the pineal gland and regulated by the SCN to be released in a circadian pattern, with endogenous levels rising at night and declining before morning [13]. Opposite of the light exposure phase response curve, administration of exogenous melatonin at night will advance the circadian rhythm, and melatonin given in the early morning will delay the rhythm [14].

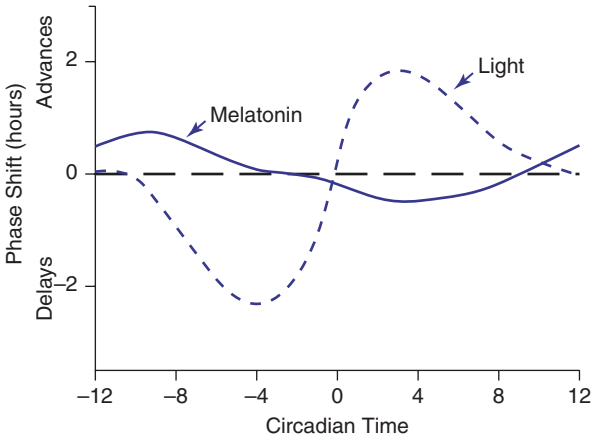


**Fig. 14.1** Phase-response curve to light and melatonin. Circadian time 0 = time of temperature nadir. (Reprinted with permission from Essentials of Sleep Medicine (first edition))

One of the many patterns generated by the circadian system is a rhythm in sleep/wake timing. The current understanding of sleep timing and regulation lies within the two-process model of continuous interaction between circadian rhythmicity (Process C) and sleep homeostasis (Process S) proposed more than three decades ago [15, 16]. Process S represents the homeostatic sleep drive and accumulates during wakefulness and declines during sleep. Process C is the endogenous biological rhythm oscillating between day and night in response to external time cues to oppose and balance the homeostatic drive to facilitate wakefulness during the day and continuous sleep during the night [17].

Circadian rhythm sleep-wake disorders (CRSWDs) arise from disruption of the circadian system or mismatch between the external sleep/wake schedule and the intrinsic circadian rhythm. This chapter focuses on the diagnosis and treatment of CRSWDs as well as providing a general overview of each disorder. The International Classification of Sleep Disorders (ICSD-3) describes six CRSWD subtypes: delayed sleep-wake phase disorder (DSWPD), advanced sleep-wake phase disorder (ASWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), irregular sleep-wake rhythm disorder (ISWRD), shift work disorder, and jet lag disorder. DSWPD, ASWPD, N24SWD, and ISWRD are considered intrinsic circadian disorders, resulting from physiologic circadian disruption or misalignment. Shift work and jet lag disorders are considered extrinsic circadian disorders because they result from misalignment secondary to externally imposed schedules. Per ICSD-3 diagnostic criteria, CRSWDs must meet the following three requirements: A) Sleep complaint is chronic and primarily due to misalignment between endogenous circadian rhythm, sleep-wake schedule, and/or social schedule. B) Circadian rhythm disruption leads to symptoms of insomnia, excessive sleepiness, or both. C) Symptoms cause clinically significant distress or impairment in functioning [18]. Each CRSWD has an additional set of specific diagnostic criteria that must be met. Assessment of sleep-wake patterns and endogenous circadian timing is important for the accurate diagnosis and treatment of CRSWDs. Sleep logs and actigraphy are essential tools for diagnosis, and measurement of circadian phase markers such as melatonin rhythms can provide additional useful information for diagnosis and treatment. Effective treatment often requires a multimodal and individualized approach of strategically timed light exposure and/or melatonin as well as behavioral modification aimed to adjust circadian misalignment.

## Delayed Sleep-Wake Phase Disorder

Delayed Sleep-Wake Phase Disorder (DSWPD) is the most commonly diagnosed CRSWD and can be challenging to differentiate from sleep-onset insomnia. It was first described in 1981 by Weitzman et al. and is characterized by sleep-wake timing that is significantly delayed compared to a conventional schedule [19]. These individuals have circadian rhythms that are entrained to 24 hours but are out of phase with the environment. Symptoms manifest as difficulty initiating sleep with delayed

sleep onset and excessive daytime sleepiness. It typically presents in adolescence and persists into adulthood [18].

## *Prevalence*

The prevalence of DSWPD has not been well-documented and is estimated between 0.1 and 9% depending on the population sampled and diagnostic criteria used. An early Norwegian study among adults aged 18–67 calculated a prevalence of 0.17% [20]. A study of New Zealand adults aged 20–59 estimated prevalence between 1.51% and 8.90% depending on the definition used [21]. The prevalence of delayed sleep phase is estimated to be between 3.3% and 8.4% in the adolescent population [22, 23]. DSWPD is extremely rare in older adults as circadian timing advances with age [24]. Approximately 10% of patients presenting with insomnia have DSWPD, and a detailed sleep history is important to differentiate the two [18].

## *Pathophysiology*

The etiology of DSWPD is unclear, and the pathophysiology may be multifactorial and include biological, psychological, behavioral, and genetic elements. Several possible mechanisms include differences in properties of the circadian oscillator, altered homeostatic regulation of sleep, increased sensitivity to light, and genetics.

Intrinsic circadian timing plays an important role in sleep-timing preference [25]. A prolonged circadian period (tau) has been found in those with evening preference, indicating a longer amount of time to complete the circadian cycle which can contribute to a delay in circadian phase [25–27]. Multiple studies have found delays in circadian timing in patients with DSWPD compared to normal sleepers as evidenced by delays in physiologic markers of circadian phase such as body temperature and melatonin rhythms [28–31]. In addition to circadian dysfunction, there may be a difference in homeostatic sleep mechanisms in these patients. Studies have found that those with DSWPD are less able to accumulate compensatory sleep drive than controls and are slower to wake [30, 32]. Environmental factors also contribute to the pathogenesis of DSWPD. Patients are exposed to more light at night and less light in the morning, which may perpetuate the delayed sleep/wake timing [33]. There is also evidence that they are more sensitive to light and have altered circadian phase shifting with larger delays in response to light exposure [34, 35]. A recent study showed that patients with DSWPD had decreased exposure to light during the phase advancing window, increasing the tendency to delay [36].

While there are multiple genetic variations that shorten the circadian period linked to a familial type of Advanced Sleep-Wake Phase Disorder (FASPD), the genetic component of DSWPD is less clear. Twin studies indicate there is a strong hereditary influence on chronotype, and the heritability of bedtime preference is

estimated to be approximately 50% [37–39]. A UK study found that a four-repeat allele length polymorphism in *Per3* is associated with DSWPD, while the five-repeat allele is linked to morning preference [40]. However, a South American study showed the opposite effect linking the five-repeat allele to DSWPD and speculate the difference may be due to variables related to latitude such as day length and temperature [41]. A familial form of DSWPD has been identified with a gain-of-function mutation of the *CRY1* gene resulting in lengthened circadian period and inheritance of DSWPD in an autosomal dominant pattern. This allele has a frequency between 0.1% and 0.6% [42]. Most recently a study of Japanese patients has shown that a low-frequency missense variant in *PER2* within the CRY-binding domain is associated with DSWPD [43].

## *Clinical Features*

DSWPD is characterized by a persistent inability to fall asleep until late in the evening and excessive sleep inertia (difficulty waking) in the morning. These patients have great difficulty adhering to conventional sleep-wake schedules and typically follow a sleep-wake schedule delayed by more than 2 hours [44]. Typical bedtimes range from 2:00 AM to 6:00 AM or even later. Patients frequently have complaints of insomnia, morning drowsiness, and tend to be more alert in the evening [19]. When patients can set their own schedules, such as during weekends or on vacation, they no longer have difficulty sleeping or waking but will prefer a later schedule. This is a fundamental feature that differentiates DSWPD from sleep-onset insomnia.

## *Diagnosis*

The ICSD-3 requires five essential diagnostic criteria that must be met to be diagnosed with true DSWPD: (A) significant delay in sleep phase that manifests as an inability to fall asleep and difficulty waking in relation to a desired or required time; (B) symptoms are present for at least 3 months; (C) patients experience improved sleep quality and duration for age when allowed to dictate their own schedule and will exhibit a delayed sleep-wake pattern; (D) sleep log and/or actigraphy for at least 7 days (preferably 14 days) including school/work days and free days that demonstrate a delayed sleep-wake pattern; (E) sleep disturbance is not better explained by other causes of insomnia and daytime sleepiness such as another sleep disorder, psychiatric disorder, or medical disorder [18].

Clinical assessment should involve a detailed sleep history and include information regarding the patient's sleep-wake schedule on work/school days as well as free days and their preferred schedule if given the opportunity to choose. To aid in the diagnosis, obtain sleep logs for at least 7–14 days, with wrist actigraphy if possible. Measurement of circadian phase biomarkers such as salivary dim light melatonin

onset (DLMO) is helpful to confirm intrinsic circadian timing and can be used to time treatments. However, it is important to note that not all patients with clinically diagnosed DSWPD will have delayed DLMO. In an Australian study of 182 DSWPD patients sampled, 57% had delayed DLMO occurring at or after desired bedtime, and 43% did not show misaligned timing of melatonin rhythm with DLMO occurring before desired bedtime [45]. The Morningness-Eveningness Questionnaire is a self-assessment of the patient's preferred sleep-wake and activity timing and can provide a reasonable estimate of chronotype and demonstrate an evening preference [46]. Polysomnography is not indicated for diagnosis and should demonstrate normal sleep architecture other than possible prolonged sleep onset latency and decreased duration if conducted during typical laboratory times [47]. Insomnia may co-occur with DSWPD secondary to conditioned arousal from time spent in bed unable to fall asleep at standard bedtimes [48]. Comorbid psychiatric disorders are common, and a thorough mental health history should be obtained [45]. Diagnosis of DSWPDs should be made only after the exclusion of other sleep disorders, psychiatric disorders, or medical disorders that can lead to the presenting sleep disturbance.

## *Treatment*

Treatment of DSWPD is primarily focused on advancing the patient's biological clock to better align with their imposed environment. Current treatment primarily relies on a combination of appropriately timed melatonin and bright light therapy. Shortly after the discovery of DSWPD, chronotherapy was developed as a therapeutic technique by progressively delaying sleep time further until the sleep period circles around the clock and reaches the desired bedtime [49]. However, caution is advised, as there have been some reports of adult patients who subsequently developed a non-24-hour sleep-wake pattern after treatment [50]. Chronotherapy is not currently a recommended treatment per the most recent American Academy of Sleep Medicine (AASM) guidelines as there have been insufficient published trials showing efficacy. Sleep-promoting agents and wakefulness-promoting agents are also not currently recommended for DSWPD, as there is little data showing efficacy [44].

The mainstay of DSWPD treatment is strategically timed administration of exogenous melatonin in the evening as recommended by AASM guidelines [44]. Low doses (0.5–3 mg) of melatonin are most effective with less concern for the residual elevation of melatonin, causing further phase delay [51, 52]. A recent randomized, placebo-controlled, double-blind trial of 0.5 mg melatonin taken 1 hour before the desired bedtime resulted in an average sleep onset advance of 34 min in patients diagnosed with DSWPD [53]. The magnitude of the phase advance response is dependent upon the timing of melatonin administration, and maximum advances occurred at 2 to 4 hours before DLMO, making the ideal time for melatonin 5 to 6 hours before habitual bedtime [48, 54].

Although there is no specific AASM recommendation for timed light therapy for adults, morning light can provide an additional benefit in entrainment when administered at the optimal time for phase advance. A combination of bright light therapy and melatonin is often used in the clinical setting. It is imperative for light therapy to be administered at the correct time to avoid further phase delay. To appropriately phase advance the patient, bright light should be delivered after the nadir of core body temperature (referred to as CBTmin), which occurs approximately 2 to 3 hours before habitual wake time [55, 56]. Exposure to light before the CBTmin can cause further delay and evening light should be restricted. Combination therapy of low dose melatonin (0.5–3 mg) 5 to 6 hours before bedtime and bright light (>5000 lux) for 30 min to 2 hours on awakening with a gradually advancing schedule results in greater long-term phase-advancing capacity than either alone [48, 57–59]. Large-scale randomized trials are still needed to fully determine the efficacy of combined light and melatonin.

## Advanced Sleep-Wake Phase Disorder

Advanced Sleep-Wake Phase Disorder (ASWPD) is characterized by sleep-wake timing that is advanced in relation to conventional schedules. These individuals typically present with an earlier natural sleep phase than the general population with earlier bedtime and wake-up time. There is also a familial subtype of ASWPD in which a strong family history of advanced sleep phase is present, and multiple causative mutations have been identified [60–62].

### *Prevalence*

There are few population studies on the prevalence of ASWPD, and true ASWPD by stringent diagnostic criteria is thought to be rare. Of 10,000 randomly sampled Norwegian adults aged 18–67 who received screening questionnaires, there were zero cases of ASWPD detected [20]. A sample of 9100 New Zealand adults aged 20–59 was surveyed, and the calculated prevalence of ASPWD ranged from 0.25% to 7.12% depending on the definition used, with a higher prevalence in older adults [21]. A recent study of 2422 new patients presenting to a North American sleep center over 10 years calculated an advanced sleep phase (ASP) prevalence of 0.33%, familial ASP prevalence of 0.21%, and estimated prevalence of ASPWD by strict definition of chronic circadian dysfunction to be at least 0.04%. Most cases presenting in young people were due to familial ASP [63]. One possible explanation for the low prevalence of ASPWD may be that it is minimally disruptive, or even advantageous, to daily life and affected individuals are less likely to seek medical attention.

## *Pathophysiology*

There is a strong genetic component to ASWPD, and those with reports of advanced sleep phase in a first-degree relative can be considered to have a familial form [64]. The first report of a familial subtype was in 1999 when three families were identified with members experiencing significant phase advances of almost 4 hours in sleep-wake, melatonin, and temperature rhythms inherited in an autosomal dominant pattern [60]. One family was found to have a missense mutation in the *PER2* gene, which disrupts the casein kinase Iε (CKIε) binding region, resulting in a shortened endogenous circadian period [62]. Multiple additional mutations have been identified in *CKIδ*, *CRY2*, *PER3*, and *TIMELESS* [61, 65–67]. Additional mechanisms include dysregulated phase resetting in response to light with a blunted phase-delay response to evening light [67].

## *Clinical Features*

Patients with ASWPD usually present with an advance of sleep-wake schedule by at least 2 hours in relation to desired or required times [44]. These individuals usually have difficulty staying awake between 6:00 PM and 9:00 PM and wake up between 2:00 AM and 5:00 AM with complaints of excessive late afternoon/early evening sleepiness and morning insomnia [48]. They also may experience chronic sleep loss due to early morning awakenings and sleep maintenance insomnia (ICSD-3). When patients are allowed to set their own sleep-wake schedule, they experience good age-appropriate sleep quality and quantity and will prefer an early schedule. The onset of ASWPD usually occurs later in life and is more common in older adults due to age-related advancing of circadian timing. However, familial types typically present with earlier age of onset.

## *Diagnosis*

The diagnostic process of ASWPD is similar to that of DSWPD. The ICSD-3 requires five essential criteria: (A) significant advance in sleep phase episode that manifests as an inability to stay awake and inability to remain asleep until desired or required conventional bedtime and wake-up time; (B) symptoms are present for at least 3 months; (C) patients experience improved sleep quality and duration for age when allowed to dictate their own schedule and will exhibit an advanced sleep-wake pattern; (D) sleep log and/or actigraphy for at least 7 days (preferably 14 days) including school/work days and free days that demonstrate an advanced sleep-wake pattern; (E) sleep disturbance is not better explained by other causes of insomnia and daytime sleepiness such as another sleep disorder, psychiatric disorder, or medical disorder [18].

Clinical assessment should involve a detailed sleep history, including the patient's sleep-wake schedule on work/school days as well as free/vacation days and their

preferred schedule if given the opportunity to choose. Diagnosis can be made based on sleep logs and actigraphy data, if feasible, for at least 7–14 days. Circadian phase biomarkers such as DLMO should demonstrate an advanced phase, and standardized chronotype questionnaires such as the Morningness-Eveningness Questionnaire should show a morning preference. These tools can be helpful in diagnosis and treatment. Diagnosis of ASWPD must be made only after the exclusion of other causes of sleep disruption, such as major depressive disorder.

### *Treatment*

The primary goal of treatment is to delay the circadian clock to the desired schedule. The AASM practice guidelines recommend light therapy as treatment. Bright light before the nadir of core body temperature results in a delay of circadian phase, and several studies have shown some efficacy with evening light treatment. In an early study, exposure to bright white light (2500 lux) for two consecutive nights in nine patients with early morning insomnia resulted in 1 to 2-hour delays in circadian biomarkers including melatonin and temperature [68]. Similarly, treatment of 24 patients with 2500 lux light for 4 hours between 8:00 PM and 9:00 PM on two consecutive nights resulted in average phase delays of 2 hours [69]. It is important to note that patients in these cohorts were not formally diagnosed with ASWPD. A study testing exposure to bright white light (4000 lux) against dim red light control (50 lux) for 2 hours before habitual bedtime in older subjects meeting ICSD criteria for ASWPD resulted in a delay in wake time of 1 hour and improved sleep efficiency and sleep time [70]. Per AASM guidelines, the largest phase-delay effects were achieved after a 12-day treatment of 2 hours of bright, broad-spectrum light (4000 lux) between 20:00 and 23:00, before habitual bedtime [44].

Exogenous melatonin administered in the morning results in circadian phase delay, and low dose melatonin upon early morning awakening can be considered as an option [71]. However, there has been no evidence demonstrating its efficacy and administration of melatonin in the morning may cause drowsiness. Therefore, morning melatonin is not currently recommended by the AASM [44]. One case study reported a patient with ASWPD who responded to chronotherapy with scheduled bedtime and wake time advancing 3 hours every 2 days until goal bedtime was reached [72]. There have been no further investigations of the efficacy of chronotherapy to date, and it is currently not a recommended treatment [44].

## Non-24-Hour Sleep-Wake Disorder

The human circadian pacemaker has an average endogenous period of slightly longer than 24 hours at approximately 24.18 hours, and entrainment of the endogenous clock to the 24-hour day-night cycle requires daily tuning to environmental cues [8]. Non-24-hour sleep-wake rhythm disorder (N24SWD) is characterized by cycles

that are typically longer than 24 hours and are not synchronized to the environment, leading to a daily drift of progressively delayed sleep-wake timing. Symptoms are often cyclical as they resolve during the time that the individual's sleep-wake schedule lines up with the 24-hour environment before continuing to drift. N24SWD primarily affects blind individuals with no light perception and, although rare, has been reported in sighted patients as well.

## *Prevalence*

N24SWD affects both blind and sighted patients. It is most common in those who are blind due to a lack of external light signals and rare in sighted individuals. The prevalence of N24SWD in either population has not been well studied. There is a high frequency of sleep disturbances in individuals who are blind and can be as high as 66% in those with complete loss of light perception [73]. In a study of 20 totally blind subjects, approximately 50% were found to have free running endogenous rhythms with a high incidence of N24SWD [74]. In a study of 127 blind female subjects, 2/3 of those with no light perception were not entrained to the 24-hour environmental cycle compared to 1/3 in those with some light perception [75]. In a cohort of sighted patients with N24SWD, 63% developed symptoms during their teenage years, and 72% were male [76].

## *Pathophysiology*

The average endogenous circadian period in humans is slightly longer than 24 hours and requires daily tuning in response to external cues to synchronize to the 24-hour environmental cycle. The strongest of these external influences is light, but other daily cues include food intake, social activity, and exercise. In blind patients who have no photic input to the central circadian pacemaker, light signaling to the SCN is disrupted, and the circadian phase resetting response to light is absent. Interestingly, not all of those who are totally blind are free-running, and this is most strikingly illustrated by evidence of some bilaterally enucleated subjects who are normally entrained [77]. This is perhaps because these individuals have endogenous rhythms that are closer to 24 hours to begin with or are more responsive to entrainment by non-photic time cues [78].

The pathophysiology of N24SWD in sighted patients is less well understood and likely multifactorial. In sighted patients with N24SWD subjected to a forced desynchrony protocol (i.e. a reasearch protocol designed to uncouple sleep-wake timing from circadian timing), it was found that they had significantly lengthened periods with a mean melatonin rhythm of 24.48 ± 0.05 hours [79]. Many individuals initially present with complaints similar to that of DSWPD but eventually develop N24SWD [76, 80]. There are reports of patients with DSWPD who subsequently

developed a non-24-hour pattern after chronotherapy [50]. There may also be a decreased ability to suppress melatonin in response to bright light and blunted plasma melatonin rhythm in sighted patients with N24SWD [81, 82]. This may be due to decreased sensitivity to light, although it is unclear if phase shifting is affected in these patients. Inappropriately timed light exposure may also contribute to the development of a non-24-hour pattern. These patients often initiate sleep at a later phase than normal patients and expose themselves to light at a time in the circadian cycle that causes further phase delay.

Lastly, there are reports of N24SWD in the context of traumatic brain injury or schizophrenia, suggesting congenital or acquired lesions that disrupt circadian structures or pathways can contribute to the development of non-24-hour sleep/wake patterns [83, 84]. No familial patterns have been observed in N24SWD, and genetic associations have not been explored.

### *Clinical Features*

Patients with N24SWD present with a progressive daily delay in the sleep-wake pattern, often with complaints of nighttime insomnia and/or excessive daytime sleepiness that alternate with periods of normal sleep. Symptomatic periods are most severe when the intrinsic biological rhythm and the extrinsic 24-hour environmental cycle are most out of phase, and sleep is occurring during the daytime. The frequency and duration of symptomatic periods depend on the magnitude of the daily delay. For example, a patient with an intrinsic period of closer to 25 hours would have a greater magnitude of delay and experience more frequent symptoms than a patient with an intrinsic period closer to 24 hours. These patients frequently have severe social disruption and may not be able to complete school or hold down a job. For most sighted patients, the average age of onset was in adolescence [76, 80]. These patients commonly start with a delayed sleep-wake phenotype and then progress to a N24 pattern [80].

### *Diagnosis*

The ICSD-3 requires four essential diagnostic criteria that must be met: (A) history of insomnia, excessive daytime sleepiness, or both, due to circadian misalignment. Sleep disturbances alternate with asymptomatic episodes of normal sleep. (B) Symptoms persist for at least 3 months. (C) Daily sleep log and actigraphy for at least 14 days (longer for blind individuals) demonstrating a sleep-wake pattern that delays each day. The circadian period is longer than 24 hours. (D) Sleep disturbance is not better explained by other causes of insomnia and daytime sleepiness such as another sleep disorder, psychiatric disorder, or medical disorder [18].

Documentation of a non-24-hour sleep-wake pattern is essential for diagnosis. Thus, sleep log and/or actigraphy must be adequately long to capture the progressively delaying pattern and should be continued for at least 14 days. Circadian biomarkers such as DLMO or the urinary melatonin metabolite 6-sulfatoxymelatonin should be obtained at two time points 2–4 weeks apart (enough time for drift to be apparent) to confirm a non-entrained rhythm. Chronotype questionnaires are less helpful as sleep-wake preferences may vary depending on which stage of the cycle.

## *Treatment*

Treatment varies depending on the underlying cause of the disorder with the common goal of entraining to a 24-hour cycle and maintenance of synchronization. For blind individuals, strategically timed melatonin is the mainstay of treatment and has been relatively well-studied [44]. The first demonstration of the efficacy of exogenous melatonin was in blind subjects with N24SWD who received placebo or 5 mg melatonin at 21:00 for 35–71 days. Four of the seven subjects receiving melatonin exhibited shortening of circadian period similar to entrainment [85]. In a crossover study with seven totally blind subjects with free-running rhythms given 10 mg melatonin or placebo 1 hour before preferred bedtime, six of seven were entrained to 24-hr cycle with daily melatonin compared to zero entrained with placebo. Entrainment persisted even once the daily dose was lowered to 0.5 mg [86]. Subsequent studies demonstrated that 0.5 mg melatonin was sufficient to initiate synchronization and was as effective as higher doses at shortening the circadian period [87, 88]. An alternative to melatonin, the selective melatonin receptor agonist Tasimelteon is approved for the treatment of N24SWD by the Food and Drug Administration. Two consecutive placebo-controlled trials in blind adults with N24SWD showed daily administration 1 hour before target bedtime for 6 months showed circadian entrainment and improved clinical outcome measures [89].

Treatment of sighted patients is less established and relies on a combination of light and melatonin based on known phase response curves. The usage of melatonin in the treatment of sighted patients has been demonstrated in several case reports with the administration of evening low dose melatonin (0.5 mg) or high dose melatonin (5 mg) with vitamin $B_{12}$ showing evidence of entrainment [81, 90]. Morning bright light therapy upon awakening has also been shown to be effective in restoring a 24-hour rhythm [91, 92]. Combination therapy with bright light upon awakening and 2 mg melatonin 2 to 3 hours before habitual bedtime or 3 mg 1 hour before bedtime successfully entrained the rhythm with a delayed phase [93, 94]. A recent case series demonstrated a combination treatment algorithm of bright light and melatonin initiated when the predicted bedtime aligns with the target bedtime. Treatment consisted of low dose melatonin (0.5–1 mg) given 2 hours before predicted bedtime and bright light therapy (10,000 lux) given for 1 hour after predicted wake time. The goal was to maintain timing, rather than inducing large phase shifts, to achieve target sleep-wake timing [80].

## Irregular Sleep-Wake Rhythm Disorder

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by the lack of a clearly discernable circadian pattern in sleep-wake behavior. This typically manifests as chronic complaints of fragmented periods of sleep that occur both during the day and night with no major sleep episode. ISWRD is more commonly observed in adults with neurodegenerative disorders or children with developmental delays.

### *Prevalence*

The exact prevalence of ISWRD is unknown, but is generally considered to be rare and mostly observed in those with neurodevelopmental or neurodegenerative disorders. It is more common in older adults, as the incidence of dementia increases [24]. There have been no reports of gender differences in ISWRD.

### *Pathophysiology*

The pathogenesis of ISWRD is not entirely understood and is likely multifactorial. It may depend on the underlying neuropathological cause of sleep disruption associated with the patient. Those affected include older patients with neurodegenerative diseases, such as Alzheimer's, adults with psychiatric disorders including schizophrenia, and children with neurodevelopmental disorders such as Angelman syndrome, Smith-Magenis syndrome, and Autism spectrum disorder [48]. One important underlying causative factor is thought to be the degeneration or disruption of SCN neurons in the circadian system. Disruptive lesions can be congenital or result from neurodegeneration or traumatic injury. This is supported by SCN ablation studies in the diurnal squirrel monkey, which resulted in the fragmentation of sleep, similar to an irregular sleep-wake pattern [95].

In the older adult population, insufficient exposure to entrainment cues such as light can contribute to the development of ISWRD. Older adults are exposed to significantly less environmental bright light relative to healthy younger adults. Those who are institutionalized are exposed to even less light overall. Older patients are also at risk of decreased transmission of light to the retina due to age-related changes such as cataracts, glaucoma, macular degeneration, and diabetic retinopathy [96]. In Alzheimer's disease, there is evidence of a reduction in numbers of vasopressin-expressing neurons in the SCN as well as an age-related decrease in melatonin secretion that can contribute to the loss of cohesive rhythms [97]. Furthermore, sleep abnormalities may precede dementia and may be an early sign of neurodegeneration as well as accelerate pathology [98].

## *Clinical Features*

ISWRD typically presents as a lack of a discernable circadian sleep-wake rhythm in which the patient sleeps in multiple short bursts lasting less than 4 hours throughout the day and night. ICSD-3 diagnostic criteria require at least three short sleep episodes with no extended sleep period during the 24-hour cycle. The longest sleep episode usually occurs between 2 and 6 AM with multiple naps throughout the day. However, total sleep time over 24 hours is typically appropriate for age [99]. Patients or their caretakers may report chronic symptoms of sleep maintenance insomnia, excessive daytime sleepiness, or both. ISWRD is more common in the setting of neurodegenerative disorders, neurodevelopmental disorders, and psychiatric disorders and can be quite challenging for caregivers.

## *Diagnosis*

Per ICSD-3, four diagnostic criteria must be met to be diagnosed with ISWRD: (A) chronic or recurrent pattern of irregular sleep and wake periods throughout the 24-hour day with symptoms of insomnia during normal sleep period at nighttime, excessive sleepiness or napping during the daytime, or both. (B) Symptoms present for at least 3 months. (C) Sleep log and/or actigraphy for at least 7 days (preferably 14 days) showing no extended sleep period and at least 3 irregular sleep episodes during a 24-hour period. (D) Sleep disturbance is not better explained by other causes of insomnia and daytime sleepiness such as another sleep disorder, poor sleep hygiene, psychiatric disorder, or medical disorder [18].

Clinical assessment should involve a detailed sleep history, and sleep logs should be obtained for at least 7–14 days and with wrist actigraphy, if available. Actigraphy may show low amplitude activity rhythms and at least three short sleep episodes throughout the day and night in a 24-hour period [48]. Caregivers may also provide valuable information regarding sleep-wake timing if the patient is unable to give accurate information. Polysomnography is not required for diagnosis. Measurement of circadian biomarkers such as melatonin and core body temperature may reveal loss of circadian rhythmicity or a low amplitude rhythm [18].

## *Treatment*

The goal of ISWRD treatment is to consolidate sleep and enhance circadian entrainment to the day/night cycle. Treatment is multimodal and includes light therapy, exogenous melatonin, and behavioral interventions. The AASM practice guidelines recommend bright light therapy for the treatment of ISWRD in older adults with dementia. In early trials, patients with dementia treated with 2 hours of 3000–5000 lux broad-spectrum light each morning for 4 weeks consolidated nocturnal sleep,

decreased daytime napping, and improved behavioral symptoms [100]. Bright light exposure of 2500 lux for 2 hours in either morning or evening is beneficial in patients with dementia and resulted in increased consolidated sleep [101]. Exogenous melatonin alone is not recommended in older patients with dementia due to the lack of evidence for efficacy and possible exacerbation of mood symptoms but may be effective in combination with light [44]. A randomized study of assisted living facilities with common areas lit with bright white broad-spectrum light (1000 lux) or dim light (300 lux) with evening melatonin (2.5 mg) or placebo found that a combination of bright light and melatonin led to improved sleep efficiency, nocturnal restlessness, and less aggressive behavior [102]. For adults with dementia, a non-pharmacological mixed modality approach consisting of morning bright light exposure (>10,000 lux), daytime physical activity, minimizing noise and light at night, and a structured bedtime routine was effective in reducing nighttime awakenings and improving daytime sleepiness [48, 103, 104]. The AASM currently does not recommend the use of sleep-promoting medications for older patients with dementia due to the high potential for adverse effects [44].

In children with neurodevelopmental delay and sleep disturbances, bright light exposure of a minimum of 4000 lux resulted in normalization of sleep in some of the children treated [105]. In a randomized controlled trial of children with autism spectrum disorder and sleep disturbances, 2 mg–10 mg of melatonin 30–40 min before bedtime improved sleep latency and total sleep time by 45 min compared to placebo [106].

## Shift Work Disorder

Shift work disorder (SWD) is a consequence of shift work that prevents individuals from adhering to a normal sleep-wake schedule. Shifts outside of the traditional 9-to-5 workday may require the worker to sleep during the day and be awake at the times of night typically reserved for sleep. Some workers may have trouble adapting to this schedule, leading to chronic circadian misalignment and impairments in sleep and wakefulness with significant negative consequences impacting health and quality of life. Shift workers suffer increased rates of cancer, higher incidence of cardiovascular and metabolic disorders, and are at a significantly higher risk for psychiatric disorders [107, 108]. Other adverse consequences of SWD include increased risk of workplace injuries and errors as well as auto accidents, which incur a high societal cost.

### *Prevalence*

Recent calculations approximate that 15–30% of the European and American workforce are shift workers [107]. An estimated 20% of US workers are engaged in shift work, and the numbers are rising in an increasingly 24/7 global economy [109].

While some workers may be able to adapt to their schedules, others experience chronic sleep disturbance and impaired function. Data obtained from the US National Health and Nutrition Examination Survey estimated a 62% prevalence of short sleep duration (< 7 hours/day) and 31% prevalence of poor sleep quality among night-shift workers with impaired activities of daily living (ADL) score and insomnia in 36% [110]. In a study of 2570 US workers, the prevalence of SWD meeting ICSD diagnostic criteria was estimated to be 10% in night and rotating shift workers [111].

## *Pathophysiology*

Shift workers live within the confines of an imposed schedule that conflicts with their endogenous circadian rhythm and the external environment. Shift schedules vary depending on industry, and overnight work is especially common in service and healthcare occupations. Common examples include night shifts, early morning shifts, evening shifts, rotating shifts, on-call overnight duty, and extended shifts of 24 hours or longer [18]. There is wide variability in the adaptability of shift workers to their schedules. It is not completely clear why some people are more affected than others, but individuals do vary in their sleep requirements and preferences for timing. For example, those with evening-oriented chronotype may prefer night shifts and be more challenged by early morning shifts, and those with morning chronotypes may be more challenged by night shifts. Age may be a risk factor for SWD, as young people are able to recover more quickly from shifts [112]. Other factors that can influence tolerance of shift work include sex, health status, and lifestyle choices [113]. The type of shift may contribute to the development of SWD. Rapidly rotating shift rotations are associated with a greater reduction in total sleep time compared to slowly rotating or permanent shifts [114]. There may also be a genetic predisposition for excessive sleepiness in some shift workers. Shift workers who reported insomnia and sleepiness during wake hours were found to be more likely to carry a long polymorphism of PER3 than those who were less sleepy [115].

## *Clinical Features*

Shift work disorder is characterized by insomnia, excessive sleepiness, or both, as a consequence of shift work with hours that interfere with conventional sleep times. Patients experience chronically decreased total sleep time due to sleep disruption and may report worsening function during waking hours. The effects of chronic sleep deprivation compounded with circadian misalignment leave many shift workers vulnerable to depression, anxiety, chronic fatigue, substance use, and cognitive deficits [116]. Symptoms usually only last for the duration of the shift work, but

some sleep difficulties may persist as shift work can be a precipitant of insomnia in certain individuals [117].

## *Diagnosis*

The ICSD-3 requires the four following criteria must be met to be diagnosed with shift work disorder: (A) symptoms of insomnia and/or excessive sleepiness, or both, accompanied by decreased total sleep time associated with a work schedule that overlaps with the usual time for sleep. (B) Symptoms have been present and associated with shift work schedule for at least 3 months. (C) Sleep log and wrist actigraphy (preferably with light exposure measurement) for at least 14 days (including work and free days) demonstrate a disturbed sleep/wake pattern. (D) Sleep disturbance is not better explained by other causes of insomnia and excessive sleepiness such as another sleep disorder, poor sleep hygiene, psychiatric disorder, or medical disorder [18].

Diagnosis is made based primarily on history. Clinical assessment should involve a detailed sleep history, including sleep schedule and habits before and after the initiation of shift work. Work history should be obtained that includes occupation with a detailed work schedule, and sleep patterns should be assessed for working and non-working periods. Cognitive difficulties, performance deficits, and safety concerns are important to identify as there is an increased risk of fatigue-related motor vehicle accidents in shift workers [118, 119]. It is imperative to assess safety risks such as excessive sleepiness while driving or operating machinery. The Epworth Sleepiness Scale is a validated and commonly used method to assess sleepiness during waking hours. Polysomnography is not required for diagnosis but can be helpful if there is a need to rule out other causes of poor sleep, such as sleep apnea.

## *Treatment*

The goal of SWD treatment is to improve sleep quality and reduce wake-time sleepiness. A multifaceted approach is most effective in addressing symptoms and promoting stable circadian entrainment, and should be tailored to the patient's individual needs and circumstance.

Non-pharmacological approaches aim to maintain circadian alignment and include keeping a comfortable sleeping environment, adhering to a regular sleep/wake and dietary schedule, scheduled napping, and strategic light exposure. There is strong evidence for napping before or during a night shift, which has been shown to improve performance and decrease accidents [120–122]. Appropriately timed light may be effective in targeting circadian misalignment and aid in adaptation to shift work schedules. Several studies have shown that exposure to bright light (2000–12,000 lux) administered in constant or intermittent schedules for various

durations before or during the first half of night shift was effective in improving alertness and tolerance of night shift [123, 124]. Avoidance of light at times that may interfere with sleep is also an important part of optimizing entrainment to night shifts. Patients can reduce bright light exposure in the morning, for example, on the drive home, with dark sunglasses [47]. Exogenous melatonin can be used to enhance daytime sleep. A meta-analysis found that administration of 1–10 mg of melatonin before bedtime is associated with increased daytime sleep duration in those who work night shifts but does not affect sleep latency time [125].

Wake-promoting agents that increase alertness may be prescribed to improve function during work hours. Modafinil and armodafinil are FDA approved for the treatment of excessive wake time sleepiness with modest improvement. In randomized trials of patients with SWD, 150 mg armodafinil taken 30–60 min before the start of the night shift improved work shift sleepiness compared with placebo regardless of shift duration [126–128]. Treatment with 200 mg modafinil before the start of night shift is more effective in reducing sleepiness than a placebo [129, 130]. Caffeine can also be an effective agent for improving alertness during work hours and has significantly fewer side effects than stimulant-type medications [109].

For patients who have trouble initiating daytime sleep, short-acting hypnotics may be used to treat insomnia and promote sleep at the desired time [109]. Benzodiazepine and non-benzodiazepine hypnotics have been found to be effective in inducing sleep in the setting of chronic insomnia, although with a risk of significant side effects such as dependence, withdrawal, and rebound insomnia [130, 131]. Short-acting hypnotics such as zolpidem and intermediate-acting benzodiazepines such as triazolam have been shown to increase daytime sleep in shift workers [132, 133]. However, these medications do not address circadian misalignment and may have serious side effects. There is evidence that suggest matching individual employee chronotypes to shift schedules reduces circadian disruption and improves sleep and general wellbeing [134]. However, this may not be practical in most work environments but should be taken into consideration, if feasible. When possible, pharmacologic agents should be used in combination with non-pharmacologic therapy, and good sleep hygiene should be a key element of any treatment regimen. Lastly, all patients should be educated on the dangers of fatigue and drowsiness while driving and should be counseled on how to recognize when they are unable to operate a vehicle.

## Jet Lag Disorder

Jet lag disorder (JLD) is characterized by temporary symptoms of insomnia and/or excessive daytime sleepiness, with a decrease in total sleep time as a consequence of circadian misalignment associated with air travel across at least two time zones. Under these circumstances, the circadian system is not given enough time to catch up to the current time zone, and there is a lag in the entrainment of the intrinsic rhythms relative to the new environment. Although JLD is generally self-limited, it can be extremely disruptive to travelers, and severe symptoms warrant treatment.

Treatment and prevention of jet lag are of particular interest to professional athletes, business travelers, and the military.

## *Prevalence*

The prevalence of JLD is unknown but likely affects many people, considering the large proportion of the population who engage in air travel globally. International and frequent travelers are especially vulnerable, especially if crossing five or more time zones [135]. All age groups and genders are at risk for jet lag. Some studies suggest that middle-aged and older individuals are more prone to having symptoms and take a longer time to recuperate [24, 136] while others have found older subjects were less likely to experience jet lag and fatigue [137]. More studies are needed to better establish a relationship between age and jet lag.

## *Pathophysiology*

The pathophysiology of JLD is relatively straightforward. Insomnia and daytime somnolence are caused by a misalignment between the endogenous circadian rhythm, homeostatic sleep drive, and local sleep-wake schedule caused by the rapid changing of time zones. A period of desynchrony persists until the circadian system is re-entrained. Symptom severity and duration are dependent on the number of time zones crossed, the direction of the time change, the extent of travel-related sleep deprivation, and individual differences in circadian adaptability [138]. Because the human endogenous rhythm is longer than 24 hours, it is easier for the circadian system to phase delay than to advance. Thus, individuals are more likely to experience jet lag and take longer to resynchronize with eastward travel due to the requirement to advance rather than delay the body's intrinsic rhythm [18].

## *Clinical Features*

Patients suffering from jet lag usually present with symptoms of insomnia and daytime drowsiness with impaired functioning within a day or two of air travel across at least two time zones. Many may also experience fatigue, headaches, irritability, cognitive difficulties, and gastrointestinal dysfunction such as indigestion, appetite changes, and inconsistent bowel function [139]. Eastward travel is associated with sleep onset difficulty as the traveler's biological time is behind the local time. Westward travel is associated with daytime and early evening sleepiness as the traveler's biological time is ahead of the local time. Symptoms tend to be more severe going from West to East and are typically compounded by general fatigue and stress caused by travel [18]. Unlike typical travel fatigue, jet lag symptoms typically do not resolve after a good night's sleep and can take several days to re-adjust.

## *Diagnosis*

The ICSD-3 requires three essential diagnostic criteria that must be met: (A) complaint of insomnia and/or excessive daytime sleepiness, accompanied by reduced total sleep time in the setting of air travel across at least two time zones. (B) Presence of associated impairment of daytime function, fatigue, or somatic symptoms such as gastrointestinal disturbance within one to two days after travel. (C) Sleep disturbance is not better explained by other causes of insomnia and daytime somnolence such as another sleep disorder, psychiatric disorder, or medical disorder [18].

The diagnosis can be made based on sleep and travel history alone, and laboratory testing is usually not indicated. However, a thorough history and physical exam may help exclude underlying sleep or medical conditions, especially in the setting of gastrointestinal complaints. In some cases of international travel across multiple time zones, prophylactic treatment can be initiated before travel to blunt the effects of jet lag, and a diagnosis will not be required.

## *Treatment*

Treatment for JLD differs for eastward or westward travel but has a shared focus on reducing symptoms of insomnia and excessive sleepiness as well as speeding up the adjustment process. Therapy is tailored to facilitate phase advances for travel eastward and delays for travel westward. Treatment for international trips across multiple time zones may begin before travel to shift the patient's schedule preemptively or after travel to accelerate entrainment.

For eastbound travel, a combination of timed morning bright light, evening low dose melatonin, and gradually advancing sleep scheduling starting 3 days before the day of travel can be employed to phase advance the circadian clock preemptively. Both light and melatonin have advancing effects when used alone and can be used together with an additive effect [140]. In one study, continuous bright light (>3000 lux) for 3 hours each day for 3 days was sufficient to produce a 2-hour phase advance [141]. Another found that four 30 min pulses of 5000 lux light alternating with 30 min ambient light produced phase advances of 1 hour per day with the addition of 0.5–3.0 mg melatonin 5 hours before bedtime [142, 143]. As sitting in front of bright light for an extended period of time can be difficult, a study determined that a single 30 min exposure of 5000 lux light with 0.5 mg melatonin 5 hours before bedtime produced phase advances of similar magnitude as longer light treatments (approximately 2 hours) [59]. If treatment is initiated after travel, melatonin can decrease the effects of jet lag and is recommended for travelers crossing five or more time zones. A comprehensive meta-analysis found melatonin doses ranging from 0.5 mg to 5 mg taken near target bedtime are similarly effective, but higher doses had greater sleep-inducing effects [144]. There are fewer studies pertaining to westbound travel, and it is much easier to phase delay than to advance. Maximizing

evening light exposure and avoiding morning light may be useful in facilitating phase delay [145]. Administration of morning melatonin could help delay timing, but its hypnotic effects may cause daytime drowsiness.

If travel is short (2 days or less), the sleep/wake schedule can be kept unchanged, and short-term use of hypnotics or wake-enhancing agents such as caffeine can be considered for the alleviation of symptoms, as circadian realignment may not be necessary or practical [109]. These agents can be used for symptom relief for more extended travel as well, but it should be kept in mind that they do not address the underlying circadian desynchrony.

## Conclusion

The circadian system regulates and synchronizes many important physiologic functions, including the sleep/wake cycle. CRSWDs arise as a consequence of the misalignment between the endogenous rhythm and the external environment. This may result from biological modifications within the circadian system or from behavioral and societal pressure that imposes a mismatched schedule. In an increasingly globalized 24-hour economy in which people are surrounded by artificial lighting and bright screens, it is more important than ever to recognize the importance of circadian disorders. Early identification and treatment are important in prevention of the negative health impacts of chronic circadian misalignment and improving patient quality of life.

**Key Summary Points**

1. The primary circadian pacemaker is located in the suprachiasmatic nucleus in the hypothalamus.
2. Most humans have an endogenous circadian period that is slightly longer than 24 hours.
3. Light is the strongest regulator of the mammalian circadian clock, and timed light exposure can be used to either advance or delay circadian timing.
4. Other non-photic time cues such as melatonin, activity, and food timing provide weaker time signals than light, but can also be used to adjust circadian timing.
5. Circadian rhythm sleep-wake disorders result when the endogenous circadian clock is misaligned with the external environment. This can occur either secondary to endogenous differences in circadian timing creating misalignment with the external environment (DSWPD, ASWPD, N24SWD, and ISWRD) or because of extrinsic factors requiring an individual to be awake during their biological night (SWD and JLD).

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