Chapter

Circadian Rhythm Disorders

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Abstract

Circadian rhythm disorders are a group of sleep conditions that involve a misalignment of an individual's internal timekeeping system with that of one's desired sleep-wake time. This desynchrony can compromise sleep health as well as the functioning of other organ system, and significantly diminish one's quality of life. There are six well-defined circadian rhythm disorders that can be classified as either intrinsic or extrinsic, based on the underlying factors that contribute to the condition. Intrinsic circadian disorders include the following: 1) advanced sleep-wake phase disorder, 2) delayed sleep-wake phase disorder, 3) irregular sleep-wake rhythm disorder, and 4) non-24-hour sleep-wake rhythm disorder. The two circadian disorders caused by external factors include 1) shift work disorder, and 2) jet lag disorder, both of which are due to behaviorally mediated misalignments of circadian system. This chapter serves to summarize these disorders, guide clinicians towards screening and evaluation of these conditions, and introduce basic treatment strategies that can be applied by non-sleep medicine clinicians.

Keywords: circadian rhythm disorder, advanced sleep–wake phase disorder, delayed sleep–wake phase disorder, irregular sleep–wake rhythm disorder, non-24-hour sleep–wake rhythm disorder, shift work disorder, jet lag disorder, melatonin, phototherapy

1. Introduction: what every clinician needs to know

The intrinsic circadian system synchronizes basic physiologic functions such as temperature regulation, appetite, and hormonal homeostasis and is responsible for the stable sleep and wake states that occur at regular times with respect to day and night. The term circadian derives from the Latin words "circa," meaning approximately, and "diem," meaning day, which emphasize that the intrinsic cycle is usually not exactly 24 hours in length [1]. The average circadian cycle length is generally 24.2 hours, which means that the cycle always requires entrainment to the environment because the day is exactly 24 hours long. Light is the most potent mechanism of entrainment, but meals and exercise also have an impact on entrainment [1–3]. Dysynchrony between a person's internal circadian system and their desired wake and sleep periods can lead to one of 6 different types of circadian rhythm sleep–wake disorders (CRSWDs). These disorders can present clinically with symptoms of insomnia and/or excessive daytime sleepiness, along with impairments in cognitive, emotional, and social functioning. A key feature of these conditions is that re-alignment of the intrinsic circadian period to the desired circadian period leads to resolution of symptoms.

CRSWDs may be due to a primary problem with the circadian system, such as altered sensitivity of the circadian system to light, and genetic and/or age-related factors that disrupt the intrinsic period of the system.

The diagnosis of CRSWDs can be difficult, due to the overlapping symptoms with other sleep disorders and medical conditions. Recognizing consistent patterns in abnormal sleep schedules is key to helping differentiate CRSWDs from other disorders. CRSWDs are primarily clinical diagnoses and use of a detailed sleep diary is an important part of the evaluation. Other objective measures such as actigraphy and melatonin measurements can supplement information obtained from the patient's history [4]. Polysomnography is usually not indicated unless there is a suspicion for a comorbid sleep disorder, such as a sleep-related breathing disorder.

Management of circadian rhythm sleep–wake disorders involves a combination of behavioral interventions, light therapy, and timed melatonin therapy. Treatment is individualized to the specific circadian rhythm sleep–wake disorder [5]. The goal of therapy is to gradually realign the patient's sleep and wake times with the desired schedule. The timing of light and melatonin therapies is critical to determining their biologic effects. The key biologic markers are the dim light melatonin onset (DLMO), which typically occurs approximately two hours prior to habitual sleeptime, and the core body temperature minimum (CBT-min), which typically occurs 2-3 hours prior to habitual wake up time. Exposure to light prior to the body temperature minimum will cause the circadian rhythm to delay (i.e. the next night, there will be a tendency to go to bed and wake up later). Light exposure after the core body temperature minimum will cause the circadian system to advance (i.e. the next night, there will be a tendency to go to bed and to wake up earlier). The effect of light is most potent when it is in the blue spectrum and administered close to the CBT-min. Melatonin has the opposite phase response relationship that light has; melatonin given prior to the CBT-min will cause the circadian rhythm to advance (i.e., the next night, there will be a tendency to go to bed and wake up earlier) whereas melatonin administration after the CBT-min will cause the circadian system to delay (i.e., the next night, there will be a tendency to go to bed and wake up later).

The International Classification of Sleep Disorders, third edition (ICSD-3), has the following three diagnostic criteria for all circadian rhythm sleep–wake disorders [6]:

1. A disrupted sleep–wake pattern, thought to be due to misalignment or malfunction of the circadian system;

2. A complaint of insomnia, excessive sleepiness, or both;

3. Suboptimal performance in an important area of functioning (e.g. occupation, education, social life, mental or physical life).

2. Classification of the circadian rhythm sleep-wake disorders

Intrinsic CRSWDs include the following: 1) advanced sleep–wake phase disorder (extreme early bird), 2) delayed sleep–wake phase disorder (extreme night owl), 3) non-24-hour sleep–wake rhythm disorder (drifting circadian rhythm), and 4) irregular sleep–wake rhythm disorder (no rhythm). The two circadian disorders caused by extrinsic factors are 1) shift work disorder and 2) jet lag disorder, both of which are due to behaviorally mediated misalignments of circadian system.

3. Are you sure your patient has a circadian rhythm sleep-wake disorder? What should you expect to find?

Circadian rhythm disorders can result in clinically significant symptoms of insomnia, excessive daytime sleepiness, and cognitive impairment. In addition,

a drastic misalignment of one's circadian clock with societal norms can often have implications for one's emotional well-being and social functioning. There are 6 major categories of circadian rhythm sleep–wake disorders which are grouped based on patterns of sleep time:

3.1 Advanced sleep–wake phase disorder (ASWPD)

ICSD-3 Diagnostic Criteria [6]:

1. An advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, (i.e. the patient feels sleepy too early and wakes up too early).

2. Symptoms are present for at least three months.

3. When the patient sleeps of his/her own accord, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode.

4. Sleep log and, whenever possible, actigraphy monitoring for at least seven days show a stable advance in sleep period. Both work/school days and free days must be included during the actigraphy monitoring period.

5. The patient's symptoms are not better explained by another current sleep, medical, neurological disorder or mental disorder.

Clinical Characteristics: ASWPD is an intrinsic defect of the circadian system in which sleep duration and quality are normal, but where sleep and wake up times are earlier than desired or socially acceptable. Generally, the intrinsic circadian rhythm period is actually shorter than normal.

Patients with ASWPD often report that they are unable to stay awake past 7 PM and tend to wake up around 2-5 AM. If a patient is able to set their own schedule they will obtain adequate sleep and feel refreshed in the morning. However, since due to social obligations they often stay up later than naturally desired while still waking early. This can lead to a sleep deficit over time that leads to daytime sleepiness.

3.2 Delayed sleep-wake phase disorder (DSWPD)

ICSD-3 Diagnostic Criteria [6]: A delay (late timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time (i.e. the patient does not feel sleepy at bed time and wakes up too late).

6. The symptoms are present for at least three months.

7. When patients sleep of their own accord, sleep quality and duration are improved with a consistent but delayed timing of the major sleep episode.

8. Sleep log and, whenever possible, actigraphy monitoring for at least seven days show a stable delay in sleep period. Both work/school days and free days must be included during the actigraphy monitoring period.

9. The patient's symptoms are not better explained by another current sleep, medical, neurological disorder or mental disorder

Clinical Characteristics: DSWPD is one of the most common circadian rhythm sleep–wake disorders, often affecting adolescents and young adults when eveningness tendencies are typically the strongest. This is a defect of the circadian system whereby the sleep/wake cycle is misaligned with the patient's desired schedule by more than 2 hours. Individuals go to sleep and wake up at substantially later times than desired, which can lead to social consequences such as chronic tardiness at work or school. Delayed bedtimes (usually between 1 and 6 AM), coupled with early awakenings to meet social/occupational/academic obligations, result in a sleep debt that accumulates over time. There is often a high prevalence of comorbid depression, and higher degrees of circadian misalignment correlate with greater severity of depression.

The intrinsic circadian period is generally longer than normal. DSWPD typically emerges during adolescence and can continue into adulthood.

3.3 Irregular sleep-wake rhythm disorder (ISWRD)

ICSD-3 Diagnostic Criteria [6]:

1. Chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period.

2. Symptoms are present for at least three months.

3. Sleep log and, whenever possible, actigraphy monitoring for at least seven days, show no major sleep period and multiple irregular sleep bouts (at least three) during a 24-hour period.

4. The patient's symptoms are not better explained by another current sleep, medical, neurological disorder or mental disorder.

Clinical Characteristics: ISWRD is characterized by a temporally disorganized sleep and wake pattern such that there are no clearly defined periods of wake and/or sleep. Multiple sleep and wake periods can occur throughout the day, and usually consist of 3 or more short intervals, approximately 1-4 hours each. The longest period generally occurs in the morning between 2 and 6 AM; however, the distribution of sleep and wake periods can vary per individual. The total sleep duration throughout a 24-hour period is generally normal for the individual's age. Because of the fragmented nature of sleep, individuals can experience frequent napping, excessive daytime sleepiness, and difficulty staying asleep at night.

3.4 Non-24 sleep-wake rhythm disorder (N24SWRD)

ICSD-3 Diagnostic Criteria [6]:

1. History of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-hour light–dark cycle and the non-entrained endogenous circadian rhythm of sleep–wake propensity.

2. Symptoms persist over the course of at least three months.

3. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, show a pattern of sleep and wake times that typically delay each day.

4. The patient's symptoms are not better explained by another current sleep, medical, neurological disorder or mental disorder.

Clinical Characteristics: N24SWD, also known as non-trained rhythm disorder, is characterized by chronic cycles of sleep and wake that are not always synchronized with the 24-hour environment. There is a gradual, but consistent drift of sleep and wake times later into the day. Attempting to maintain a regular sleep–wake schedule can lead to symptoms of excessive daytime sleepiness, chronic fatigue, early morning awakenings and insomnia. These symptoms alternate with days to weeks in which the patient is asymptomatic, owing to the patient's endogenous circadian system coinciding with the external 24-hour cycle. Napping is common, and patients often report impairment of social and occupational functioning due to non-entrained sleep–wake schedule.

N24SWD occurs most often in blind individuals. Onset of symptoms usually occurs in 2nd or 3rd decade of life, and men are disproportionally affected compared to women at a ratio of >2: 1 [7].

3.5 Shift work sleep-wake disorder (SWD)

ICSD-3 Diagnostic Criteria [6]:

1. Insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps with the usual time for sleep.

2. Symptoms are present and associated with the shift work schedule for at least three months.

3. Symptoms cause clinically significant impairment in mental, physical, social, occupational, education, or other important areas of functioning.

4. Sleep log and, whenever possible, actigraphy monitoring for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern.

5. The patient's symptoms are not better explained by another current sleep, medical, neurological disorder or mental disorder.

Clinical Characteristics: Individuals who work night shift experience difficulty with sleep and alertness at desired times, and are at greater risk for the variety of adverse health outcomes associated with poor sleep. Shift workers generally report 30-90 minutes less sleep compared to those not working shifts, and their sleep quality tends to be more fragmented and of poorer quality. Shift workers also experience difficulty falling and staying asleep, with as many as 20% of shift workers having clinically significant insomnia [8]. During waking hours, night shift workers are more prone to increased sleepiness, decreased neurocognitive function and more significant changes to mood than their non-night shift counterparts.

3.6 Jet lag disorder (JLD)

ICSD-3 Diagnostic Criteria [6]:

1. Insomnia or excessive daytime sleepiness associated with a reduction of total sleep time coinciding with jet travel across at least two time zones

2. Impaired daytime function, general fatigue, or somatic symptoms that begin within two days of travel

3. The sleep disturbance cannot be explained by another disorder.

Clinical Characteristics: JLD occurs when an individual travels through time zones faster that the endogenous circadian rhythm can adjust, resulting in desynchrony between the external light–dark cycle and one's internal clock. Symptoms of JLD include difficulty falling and staying asleep, excessive daytime sleepiness, generalized fatigue, impaired daytime performance, and various somatic symptoms (most commonly gastrointestinal) that begin 1 to 2 days post-travel [8].

In addition to number of time zones traveled, the severity of jet lag is affected by the direction of travel. Eastward travel leads to more difficulty with falling asleep and is more difficult to adjust to, while westward travel is more disruptive to sleep maintenance.

4. How and/or why did the patient develop a circadian rhythm sleep-wake disorder? Which individuals are of greatest risk of developing a circadian rhythm sleep-wake disorder?

4.1 Advanced sleep-wake phase disorder (ASWPD)

Genetic studies have shown possible links to mutations in the *PER2* and *CSNK1D* clock genes, both of which are inherited in autosomal dominant pattern [2, 3]. There is an estimated 1% prevalence, with males and females being equally affected. Older adults are more likely to have advanced tendencies. Other contributing factors include decreased responsiveness to evening light, and increased responsiveness to morning light, both of which can shift the sleep–wake cycle earlier than desired.

4.2 Delayed sleep–wake phase disorder (DSWPD)

The pathophysiology of DSWPD is multifactorial [2, 3] l. It is hypothesized that certain exogenous factors, such as increased exposure to evening light and greater sensitivity to evening light may play a role in development of DSWPD. Genetic factors may play a role, but their exact contribution is less understood than is the case for ASWPD.

DSWPD typically emerges during adolescence and can continue into adulthood. Males and females seem to be affected equally. Peak age appears to be 21 years old in males and 17 years old in females. There is a large variability in its reported prevalence, with population study estimates ranging from <1% up to 10% [1–3]. Patients with hepatic cirrhosis are also affected at much higher rates (33%).

4.3 Irregular sleep-wake rhythm disorder (ISWRD)

ISWRD is most commonly seen in individuals with neurodegenerative conditions, particularly those with Alzheimer's disease and late-afternoon sundowning [1–3]. It is also more common in those with traumatic brain injury, in children with developmental delay, in patients with schizophrenia, and particularly in patients who are institutionalized. It is hypothesized that intrinsic circadian dysfunction, coupled with decreased exposure to external synchronizing agents such as light and social activity, are factors in ISWRD.

4.4 Non-24 sleep-wake rhythm disorder (N24SWRD)

The etiology of N24SWD is related to disruption of the portion of the circadian system responsible for capturing photic stimuli in the retina. Pathologies that lead to vision loss often but not necessarily impact this system. Thus, N24SWD occurs most often in blind individuals, with reports of 50% of blind patients diagnosed with N24SWD and up to 70% of blind individuals having symptoms of chronic sleep disturbance [2, 3, 7]. Men are disproportionally affected compared to women at a ratio of >2:1. N24SWD is rare, but has been reported, in sighted individuals. In sighted individuals, N24SWD is thought to be a severe form of delayed sleep phase disorder where entrainment to light can no longer be effective [7].

4.5 Shift work sleep-wake disorder (SWD)

The mechanism behind SWD is thought to be governed by disruptions of 2 physiologic processes [1–3]. The first is related to one's homeostatic drive for sleep, which increases throughout wakefulness. The second is one's intrinsic rhythmic oscillations for sleep and wake periods, which is governed by the circadian pacemaker. This latter process is calibrated by environmental clues such as light. Both the homeostatic process and the circadian process are disrupted in SWD.

Individuals at greatest risk for SWD are those that work rotating night shifts, rather than permanent night shifts, because they are never able to adapt to a stable sleep–wake pattern [8]. In addition, those with other sleep comorbidities can have synergistic effects of sleep disturbance, which lead to symptomatic worsening.

4.6 Jet lag disorder (JLD)

JLD results from desynchrony between the external light–dark cycle and an individual's internal clock when travel across time zones occurs more quickly than the endogenous circadian rhythm can adjust. The prevalence of this condition is poorly defined [8]. Factors that affect jet lag severity include the direction of travel and number of time zones traveled, the person's ability to sleep during travel, individual variations in circadian timing, presence of light cues at destination, and intake of alcohol and caffeine.

5. What diagnostic studies will be helpful in making or excluding the diagnosis of a circadian rhythm sleep-wake disorder? What other diseases can mimic circadian rhythm sleep-wake disorders?

5.1 Advanced sleep-wake phase disorder (ASWPD)

ASWPD is a clinical diagnosis and should be suspected in individuals who have a history of early sleep onset and wake times. It is important to obtain a detailed sleep history that addresses sleep patterns, napping habits, and daytime symptoms of sleepiness, cognitive changes, or mood changes. Targeted questions should be asked about difficulty falling or staying asleep and sleep quality both during the patient's current schedule and during times when he/she has followed the preferred schedule. Obtaining collateral history from a bed partner is often useful.

Patients with suspected ASWPD should keep a sleep log for at least 7 days, preferably 14 days, including both weekdays and weekends (**Figure 1**). Actigraphy is helpful to supplement the sleep diary, especially if the history is unreliable. Melatonin levels, through salivary or plasma sampling, may show early melatonin onset or earlier phase of melatonin metabolite excretion via urinary 6-sulfatoxymelatonin, although these tests are not widely available for clinical purposes [2, 3, 9].

5.2 Delayed sleep-wake phase disorder (DSWPD)

DSWPD is a clinical diagnosis and should be suspected when individuals report consistent bedtime and wake times that are significantly later than social norms. Bedtimes are often more informative than wake times, which are usually dictated by social or work/school obligations. It is also helpful to ask about sleep patterns during weekends, and during unrestricted periods such as vacations, when patients are able to sleep based on their own circadian preference (**Figure 2**). Sleep logs of at least 7 days, including both school/workdays and weekends, are needed to identify specific patterns [9]. It is important to inquire about other social factors, such as caffeine use later in the day, or excessive use of light-emitting devices before bedtime, which can also delay sleep onset.

Wrist actigraphy is another means of obtaining more quantitative data [9]. If the actigraph has a photo sensor it can provide information about the correlation between an individual's light exposure and sleep time. Polysomnography is not typically indicated, unless there is clinical suspicion for another comorbid sleep disorder, such as sleep-disordered breathing. Salivary melatonin assays are available; however, these assays are used primarily as research tools and not for clinical diagnosis.

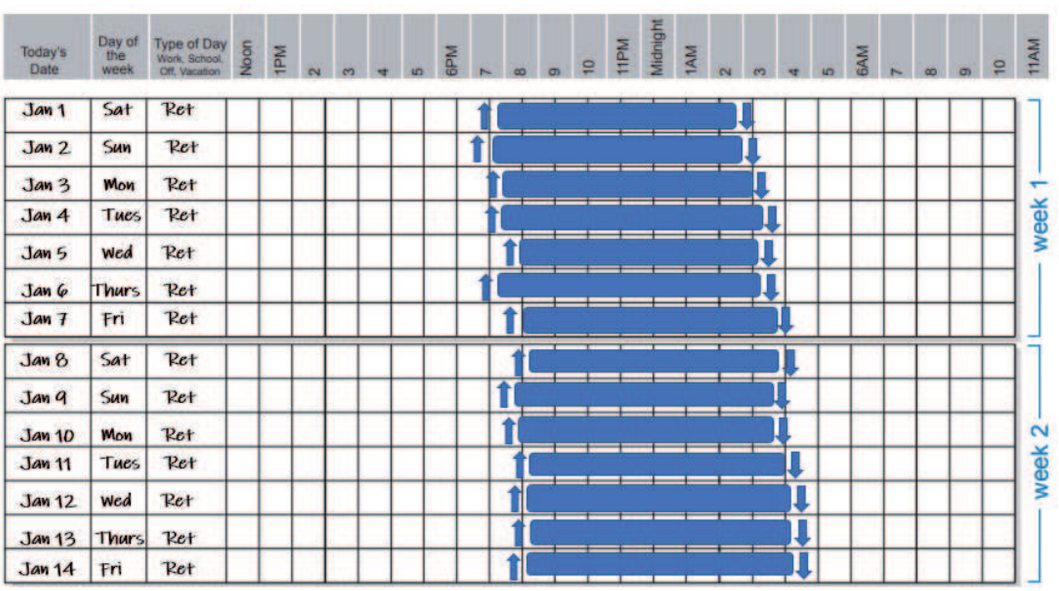

Figure 1.
This 14-day sleep diary of a patient with advanced sleep–wake phase disorder (ASWPD) depicts an early sleep onset (7-8 pm) and early wake time (3-4 am). The total duration of sleep time (shaded box) remains normal at 7-8 hours. Individuals with ASWPD usually do not have symptoms if they are allowed to sleep per their preferred schedule; however, when tasked with staying up later than their usual bedtime, they can have significant difficulty. This circadian rhythm is more prevalent in older adults who may not have the same work or school obligations ("ret" represents "retired") that can contribute to other circadian rhythm disorders, such as delayed sleep–wake phase disorder.

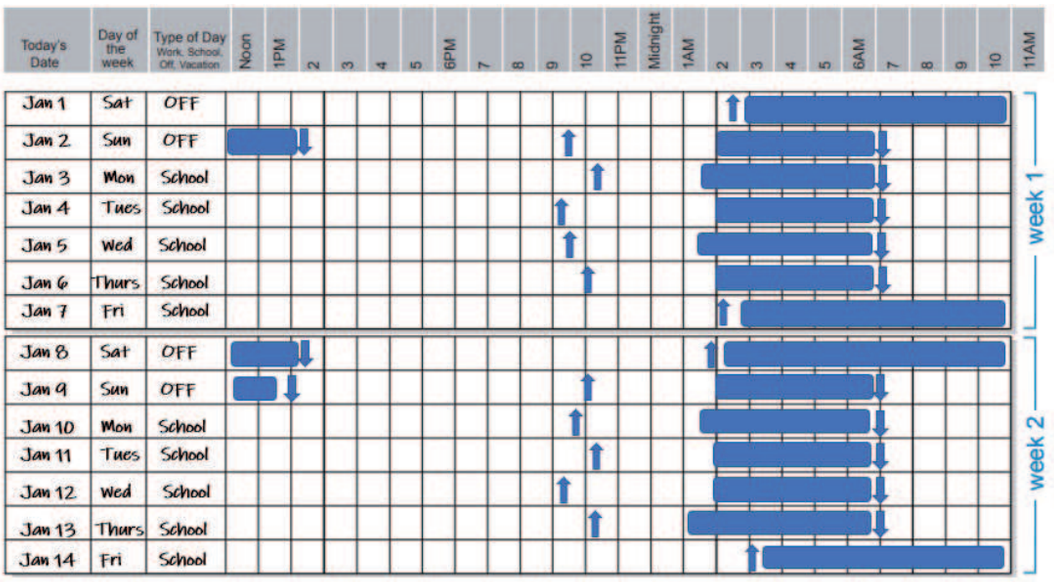

Figure 2.
This 14-day sleep diary of a patient with delayed sleep–wake phase disorder (DSWPD) depicts variable sleep depending on the day of the week. The upwards arrow indicates "time in bed" while the downwards arrow indicates "time out of bed". The shaded area represents sleep time of the patient. For example, in this diagram, the individual goes to bed between 9 and 10 pm on school days but is not able to sleep until 2-3 am. Due to his fixed school start time, he has to get out of bed between 6 and 7 am, leaving only 4-5 hours of sleep time (shaded box). However, on weekends (Friday and Saturday nights), he goes to sleep at his desired time of 2-3 am and wakes up at his desired time between 1 and 2 pm, accounting for a total sleep time of 10-11 hours. This variation in sleep pattern, based on day of the week, is classic for DSWPD, and results in the symptoms described by those with this condition.

5.3 Irregular sleep-wake rhythm disorder (ISWRD)

The diagnosis of ISWRD is made by clinical history, with supplemental information from wrist actigraphy. There must be a reported chronic or recurrent pattern of irregular sleep and wake episodes throughout a 24-hour period, with a minimum of 3 cycles occurring during that time (**Figure 3**). A sleep log, and/or actigraphy must document these cycles for at least 7 days (preferably 14 days), and symptoms must be present for at least 3 months [9].

Polysomnography is not usually indicated, unless there is concern that the sleep disturbance is better explained by another disorder (e.g., a sleep-related breathing disorder).

5.4 Non-24 sleep-wake rhythm disorder (N24SWRD)

Sleep diary and actigraphy are important in confirming a non-entrained sleep pattern and will also show a gradual drift of onset and offset of the sleep–wake rhythm (**Figure 4**). In order to appreciate the drift, this data should be obtained for at least 2 weeks, and symptoms should be present for at least 3 months [9].

Other measurements such as continuous core body temperature or serial measurements of melatonin can be confirmatory as they also exhibit a similarly non-24-hour drifting rhythm. However, these procedures are not required to make the diagnosis of N24SWD.

Attention should be paid to distinguish N24SWD from DSWPD, as these patients can display a similar evening phenotype and up to 25% of N24SWD are often initially misdiagnosed as DSWPD [2, 3, 9].

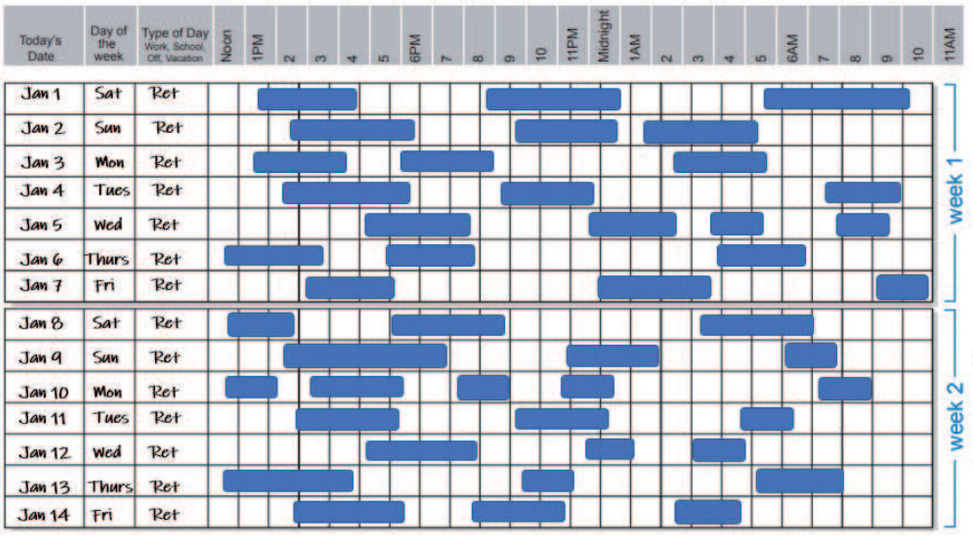

Figure 3.
This 14-day sleep diary of a patient with irregular sleep-wake rhythm disorder (ISWRD) depicts an irregular pattern of sleep throughout each 24-hour period. During each day, there are at least 3 sleep cycles occurring in a recurrent, but irregular fashion. The total sleep duration (shaded box) is usually normal for an individual's age, however there is no clearly defined pattern. This disorder is more prevalent in older individuals and in those with dementia.

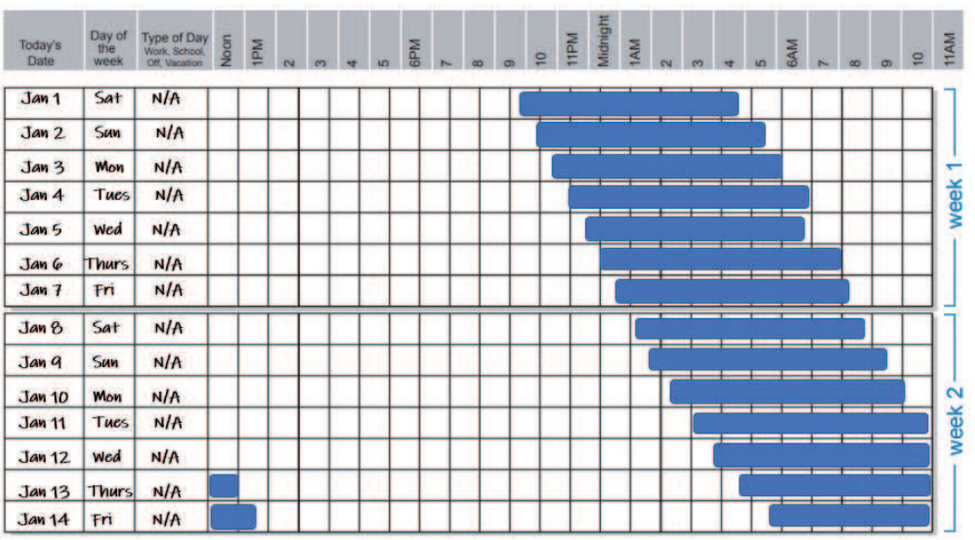

Figure 4.
This 14-day sleep diary of a patient with non-24 sleep–wake phase disorder (N24SWPD) depicts a gradual drift in onset and offset of the sleep duration (shaded box), usually by 30 minutes each day. In order to best appreciate this drift, a sleep diary or actigraphy should be obtained for at least 2 weeks, and ideally more if possible. This circadian rhythm disorder is most prevalent in individuals who are blind.

5.5 Shift work sleep-wake disorder (SWD)

SWD is best assessed through careful sleep history and sleep diary. Particular attention should be paid to a patient's occupation, history with shift work disorder with prior jobs, and impaired task performance at work. Factors specific to the patient's home environment (i.e. lack of dedicated dark space for sleeping, noise levels during the day, etc.) can further reduce the likelihood that the patient can obtain restorative sleep. The clinical history should also inquire about features of other comorbid sleep, medical, and mental disorders. A sleep diary should be obtained for at least 2 weeks and should capture both work and non-work days [9]. Validated questionnaires, such as the Insomnia Severity Index and Epworth Sleepiness Scale, can be used but are not required to diagnose SWD.

Wrist actigraphy, especially when performed with an actigraphy that includes a photosensor, can better quantify sleep duration. There is no need for polysomnography unless there is a clinical suspicion for a comorbid sleep disorder, such as a sleep-related breathing disorder. Melatonin sampling is done in research settings, but is not routinely used in the clinical setting.

5.6 Jet lag disorder (JLD)

Clinical history is the most important tool. The clinician should specifically obtain information about number of time zones crossed and the timeline of symptom occurrence. JLD is often confused with travel fatigue since there are many overlapping symptoms; however, the distinction is that travel fatigue is not dependent on the number of time zones traveled and tends to resolve quicker.

Since JLD is transient, and clinical history is usually clear, there is typically no role for formal diagnostic testing.

6. If you decide the patient has a circadian rhythm sleep-wake disorder, how should the patient be managed?

6.1 Advanced sleep-wake phase disorder (ASWPD)

Bright light therapy in the early evening is the primary treatment for ASWPD, with the goal to delay the circadian phase so it is better aligned to desired sleep and wake times [5, 9]. Patients should use a bright light that filters out ultraviolet rays (2,500 to 10,000 lux) for 1-3 hours per day, starting at the time when they first experience sleepiness in the evening (usually around 7-9 pm). This should be done to gradually delay bedtime by 1-2 hours each day until desired times are met (**Figure 5**).

There is no strong evidence to support pharmacologic therapy in ASWPD. Melatonin in the morning can theoretically shift the clock to a later phase, however the sedating effect of melatonin often limits morning use. Early morning hypnotics to resume sleep can lead to daytime grogginess and hangover effect and thus are generally discouraged.

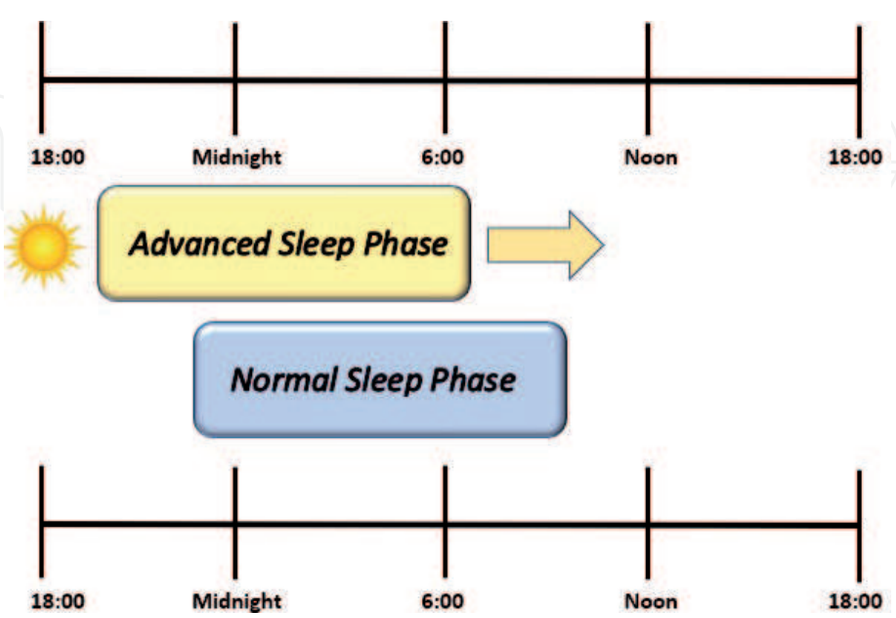

Figure 5.
For individuals with advanced sleep–wake phase disorder (ASWPD), bright light therapy should be given for 1-3 hours per day in the evening starting at the time of sleepiness. This will gradually shift the sleep time until the desired schedule is met.

6.2 Delayed sleep-wake phase disorder (DSWPD)

Management of DSWPD consists of *behavioral modifications* to realign one's circadian system with desired sleep–wake times, and concurrent *melatonin* use and *light* therapy. Easily modifiable behaviors should be targeted first. These behaviors include avoiding daytime naps, eliminating excessive use of caffeine and/or alcohol, reducing stimulating activity, and minimizing light (particularly blue light) exposure 2 hours prior to bedtime.

For those who fail to respond to behavioral therapies alone, timed melatonin can supplement these behavioral modifications. One reasonable approach would be to take melatonin daily, approximately 3-5 hours prior to desired sleep time [5]. Doses may vary from 0.5-5 mg, though it is best to use the lowest effective dose. Melatonin dose and timing can be strategically adjusted based on clinical response. Relapse tends to occur in high rates (80-90%) once melatonin is discontinued [3, 5].

Morning light therapy can be coupled with the above interventions. Commercial light boxes that either contain a broad spectrum of white light or narrow spectrum of blue light (2,000-10,000 lux) should be used every morning between just after typical wake-up time, with gradual advancing of the sleep–wake time until the desired time is reached [5, 9]. Care should be taken to avoid light exposure earlier than 2-3 hours before the habitual wake up time because light prior to the core body temperature minimum may cause further delays in circadian phase (**Figure 6**).

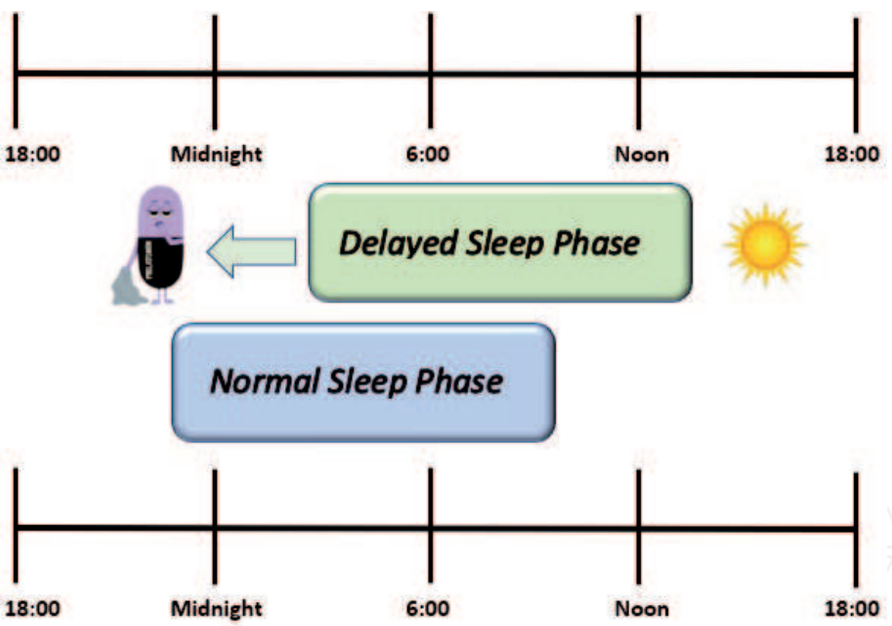

Figure 6.
For individuals with delayed sleep–wake phase disorder (DSWPD), treatment can consist of low-dose melatonin (to be taken ~3-5 hours prior to desired sleep time), along with phototherapy in the morning upon awakening. This combination can cause gradual advancement in sleep phase.

6.3 Irregular sleep–wake rhythm disorder (ISWRD)

Treatment of ISWRD involves using behavioral strategies to restructure an individual's daily routine, and to optimize sleep hygiene to better consolidate sleep times and improve daytime alertness. It is important to create a cognitively enriched and socially interactive environment during the day to maintain alertness and prevent excessive napping. At night, measures should be taken to reduce noise and light, and to prevent sleep disturbances caused by other factors (e.g., nocturia).

Light therapy remains the most effective intervention during the day. Exposure to 3,000-5,000 lux of light for at least 2 hours in the morning has been shown to improve daytime alertness, reduce napping, and consolidate nightly sleep [5].

Melatonin can also be used for management of ISWRD, though positive results with melatonin use are less consistent than with treatment of other CRSWDs. Melatonin doses of 1-5 mg can be used 30 min prior to bedtime to facilitate sleep, and melatonin is more effective if used in conjunction with light therapy [3, 5]. Controlled-release formulation can be more effective than immediate release in this specific patient population with ISWRD.

6.4 Non-24 sleep-wake rhythm disorder (N24SWRD)

Treatment for N24SWD includes attempting to re-synchronize the circadian pacemaker using behavioral approaches and pharmacologic therapy. Education regarding proper sleep hygiene and maintenance of regularly scheduled timing of meals, social activities and physical exercise is important.

Tasimelteon, a melatonin agonist with affinity for the MT1 and MT2 receptors, is Food and Drug Administration (FDA) approved for use in N24SWD [5]. Melatonin can also be used to achieve gradual re-alignment. Higher doses (3-10 mg) may be given 1-2 hours prior to the desired bedtime for the first month. Entrainment usually occurs within 5-10 weeks, after which low-dose melatonin (0.5-1 mg) should be maintained to prevent relapse [5, 7].

Less robust evidence exists for bright light therapy, though it has been shown to be effective in sighted individuals with N24SWD and can be used in the early morning after awakenings.

6.5 Shift work sleep-wake disorder (SWD)

Management of SWD should first start with changes to work schedule, if possible, with adjustments to sleep hygiene. A regular daytime sleep schedule that can be followed, even during non-working days, is recommended to promote stability to the circadian system. This can be organized around an individual's personal schedule, but should ideally incorporate at least a 5 to 6-hour block of uninterrupted sleep. The sleep environment should be optimized to reduce sound, light, unfavorable temperatures and other factors that can interfere with sleep. Light blocking window shades can be used, and a temperature setting between 65 and 70 degrees Fahrenheit is optimal.

While at work, individuals can use continuous exposure to high-intensity light (2,000-10,000 lux) for as little as four 20-minute periods during the first part of the nigh [8] t. Use of blue light-blocking goggles in the morning and general avoidance of morning light help the circadian rhythm remain adapted to the shift work schedule. Additionally, short naps (<45 minutes) prior to the start of the work shift are a low-risk intervention that can be used to promote wakefulness during the shift.

If these behavioral measures fail, medication therapy is the next step. Modafinil (200 mg) and armodafinil (150 mg) are FDA approved for shift work disorder and can be used during the first part of the night [5, 8]. Small doses of caffeine (100-250 mg, equivalent to a small cup of coffee) can also be used during the first part of the night. Short-acting hypnotics such as zolpidem and zaleplon can be used to promote sleep during the daytime; use of hypnotics must be introduced cautiously to prevent nocturnal grogginess (during work hours). Exogenous melatonin 30 min prior to desired bedtime can be used, although the evidence for this is poor [5].

6.6 Jet lag disorder (JLD)

The treatment strategy depends on the length of trip, number of time zones traveled, and direction of travel [9]. Trips less than 3 days are usually too short to create problematic jet lag symptoms. Treatment planning is best done in anticipation of travel.

For eastward travel on trips longer than 3 days and up to 7 time zones, a strategy using timed light exposure and melatonin can help advance the circadian rhythm (making natural bedtime and wake time earlier) to the new time zone. Bright light therapy can be started up to 3 days prior to departure to start the advancing process. Individuals should wake up about 1 hour prior to usual wake-up time and expose themselves to bright light for at least an hour. Upon arrival at destination, strategic light exposure throughout the afternoon and light avoidance during the early morning can help with this circadian realignment. The specific timing of light exposure is based on when the patient's habitual core body temperature minimum (CBT-min) occurs, which is usually 3 hours before habitual wake-up time. Light exposure after the CBT-min causes circadian phase advancement, whereas light exposure before the CBT-min causes a circadian phase delay and is thus counterproductive for eastward travel [8].

Timed melatonin (3-5 mg) taken at the desired destination bedtime can be used concurrently with prescribed light exposure. Melatonin should first be taken on the evening of arrival and continued for up to 5 days. Hypnotics have been used by patients during travel, but these medications can lead to impaired daytime performance, and thus are generally not recommended for management of JLD. Caffeine can help mitigate daytime sleepiness. Other stimulants (e.g. modafinil, armodafinil) can offset daytime sleepiness though these medications are not FDA approved for JLD. For eastward travel that crosses more than 8 time zones, it is often easier to pursue a circadian phase delay, rather than a circadian phase advance, to mitigate symptoms of JLD. This approach generally involves seeking out early morning light at the destination and avoiding light exposure in the afternoon.

Westward travel requires a delay in the circadian rhythm (later bed times and wake times) to adjust to the destination time zone. It is advised to seek bright light before the calculated CBT-min at the destination (based on the home time zone). For example, if one's habitual wake up time in Boston is 8 am Eastern Standard Time (EST), the habitual CBT-min will be at 5 am EST. If that individual travels to Westward to Hawaii (5-hour time zone delay), the CBT-min will occur at midnight EST, thus bright light exposure should be given prior to that time. Melatonin or hypnotics are generally not required in JLD associated with westward travel.

Resources such as www.jetlagrooster.com and the British Airways jet lag advisor [10] can help individuals plan light and melatonin exposure including in preparation for travel.

7. How do patients generally respond to treatment? What other considerations exist for patients with circadian rhythm disorders?

Treatment of circadian rhythm sleep wake disorders can often be challenging, and requires an individualized and multimodal approach, incorporating behavioral strategies such as directed light exposure, and appropriately timed melatonin. Overall effectiveness can be improved by combining these measures with chronotherapy, which gradually and progressively shifts the circadian clock.

Patients tend to respond well initially, however often require significant personal investment to maintain their newly desired schedule, and relapse to prior sleep schedule is not uncommon. It is essential to have the support of family, friends, teachers and coworkers to establish and maintain a sustainable new sleeping schedule.

When treating circadian rhythm sleep wake disorders, it is important to optimize the treatment of other comorbid medical conditions, especially psychiatric and mood disorders. This is especially true in adolescents and older patients. The importance of addressing sleep hygiene and one's sleep environment cannot be overstated as a critical component of treatment.

The treatment of CRSWDs remain a challenge, in part because of the scarcity of large, multicenter placebo-controlled trials using phototherapy and pharmacotherapy. However there have been recent rapid advances in our understanding of the genetics of circadian rhythm regulation, which may lead to improved diagnostic tools and treatments. For example, technology involving DNA manipulation has been used to generate Cry1/Cry2 knockout animals to further study the expression of specific genes on circadian function [11]. This opens up avenue for new therapeutic approaches in many disorders, specifically neuropsychiatric conditions, associated with circadian rhythm disturbance.

8. Conclusions

Circadian rhythm disorders are common conditions that occur as a result of misalignment between an individual's intrinsic time-keeping system, and extrinsic cues. There are usually multifactorial contributions, including genetic influences, and behaviorally induced elements. Effective treatment approaches largely revolve around strategically timed melatonin and phototherapy to shift one's sleep phase to a more desired time. Consultation with a sleep medicine clinician may be helpful if symptoms persist, or to clarify a suspected circadian rhythm disorder.

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