CIRCADIAN RHYTHM DISORDERS: UPDATE ON DIAGNOSIS AND TREATMENT

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Overview

Circadian rhythms are the near-24 hour rhythms observed in nearly all organisms. While the sleep-wake pattern is the most readily apparent of these rhythms, multiple other behaviors and physiologic processes also follow 24 hour patterns. In mammals the primary pacemaker regulating these rhythms is the suprachiasmatic nucleus (SCN), located in the hypothalamus. These rhythms are maintained at a cellular level through a set of core 'clock' genes that form a transcription-translation feedback loop. This molecular clockwork mechanism is present both in the SCN, and in tissues throughout the body, resulting in central and peripheral oscillators. The mammalian circadian clock can be reset in a time-of-day dependent manner in response to multiple time cues, with the strongest being light and melatonin.

Circadian rhythm sleep-wake disorders (CRSWDs) result when there is misalignment between the internal circadian clock and the surrounding environment, either due to a biological predisposition, or due to social/environmental constraints (e.g. shift work and jet lag). Symptoms of CRSWDs include excessive sleepiness and/or insomnia, depending on the time of day. Evaluation should include, at a minimum, sleep logs and/or actigraphy for at least 14 days to confirm the diagnosis. Additional information can be obtained through chronotype questionnaires and/or physiological measures such as salivary melatonin. Polysomnography is generally not indicated, unless there is additional suspicion for an underlying sleep disorder such as sleep apnea.

Delayed Sleep-Wake Phase Disorder

Individuals with delayed sleep-wake phase disorder (DSWPD) exhibit a significant delay in the sleep-wake pattern with respect to their desired sleep-wake timing. Bedtimes typically range from 2 am to as late as 6-7 am depending on the severity. Individuals will often present with symptoms of difficulty initiating sleep. However unlike a primary insomnia, they are able to fall asleep and stay asleep without difficulty if they wait to attempt to sleep until their natural bedtime, and as a result, often have significant daytime sleepiness from then attempting to wake at conventional times. Prevalence ranges from 1.5-16%, depending on the population study and the definition used, with the disorder generally more common among younger adults (1, 2).

The underlying cause of DSWPD is currently unknown, however there are several potential possibilities. First social and environmental factors may contribute. Exposure to light at night can delay the circadian clock, while exposure to light in the morning advances the circadian clock. Staying up later and sleeping later may result in increased exposure to delaying light and decreased exposure to advancing light (3). Individuals with DSWPD may also be more sensitive to the delaying effects of light or less sensitive to the advancing effects of light (4).

Treatment of DSWPD relies on timed exposure to light and melatonin, in order to advance the circadian clock. Melatonin (0.5 mg) is typically administered ~5 hours prior to the current habitual bedtime. Bright light therapy is typically administered for 30-120 minutes after awakening. Behavioral interventions, including maintaining regular sleep-wake schedules and minimizing evening exposure to bright light are also important (5).

Advanced Sleep-Wake Phase Disorder
Patients with advanced sleep-wake phase disorder (ASWPD) have a significant advance in their sleep-wake pattern, with habitual bedtimes typically around 6-9pm. They will often present with symptoms of early morning awakenings, however unlike a typical sleep maintenance insomnia they are able to extend their total sleep time by going to bed earlier. When attempting to maintain a conventional sleep-wake schedule they will often develop hypersomnia because of an inability to sleep in. The diagnosis is confirmed with sleep logs and/or actigraphy demonstrating an advance in the sleep-wake pattern. Obtaining biomarkers such as the timing of the salivary dim light melatonin onset can help distinguish between insomnia and ASWPD (1).

At least some cases of ASWPD are hereditary, with familial mutations noted either in casein kinase 1□, or the phosphorylation site of this kinase on the circadian clock protein hPER2 (6-9). The net result of this mutation is a molecular clockwork that completes a cycle in under 24 hours, resulting in a constant advance of the circadian clock. For individuals without a strong family history, other possible causes may include either increased sensitivity, or increased exposure to early morning light, which advances the circadian clock.

Treatment of ASWPD depends primarily on the use of bright light therapy in the biological evening (typically around 7-9pm), when it is most likely to delay the circadian clock, allowing for later bedtime and rise times (5).

Irregular Sleep-Wake Rhythm Disorder
Sleep-wake patterns in irregular sleep-wake rhythm disorder (ISWRD) consist of disorganized sleep, typically with at least 3 distinct sleep periods, with no clear day-to-day pattern. Total sleep times within a 24 hour window are normal for age however. Symptoms include either insomnia or excessive sleepiness, depending on the time of day of presentation. Due to the underlying cause of the disorder, patients with ISWRD are often unable to complete sleep logs, so diagnosis is best made using actigraphy for at least 14 days or by having caregivers complete sleep logs (1).

ISWRD is frequently seen in children with neurodevelopmental disorders associated with hypothalamic or visual dysfunction, or in adults with neurodegenerative disorders. Individuals with traumatic brain injury can also develop ISWRD. In all cases, the likely etiology is the combination of a poorly functioning circadian pacemaker, in conjunction with weak environmental time cues (10).

Treatment of ISWRD focuses on strengthening environmental time cues through mixed modality therapy. This includes daytime bright light exposure and behavioral strategies to reduce time in bed and increased daytime activity. In addition, in children the addition of melatonin at bedtime has been effective, but this is not recommended in adults with dementia (5).

Non-24-Hour Sleep-Wake Rhythm Disorder
Patients with non-24 hour sleep-wake rhythm disorder (N24SWD) are unable to follow a 24 hour schedule, instead typically following a schedule >24 hours. As a result, they will present with periods of severe insomnia and daytime sleepiness, alternating with patterns of normal sleep, as their sleep-wake pattern drifts progressively later each day. Diagnosis is best made with actigraphy for at least 14 days, preferably longer to demonstrate the daily pattern of drift.

There are two main groups of individuals who present with N24SWD. The first category includes individuals who are blind, and have lost visual input to the SCN. As such, they are no longer able to receive the daily resetting signals from environmental light, and follow their own internal rhythm, which is typically >24 hours. Of note, not all blind individuals develop N24SWD. The other category of individuals are those with normal sight. These individuals often initially present with DSWPD, and eventually begin to drift later and later. There is some evidence that these individuals have an endogenous circadian period that is significantly longer than 24 hours, which may contribute to the difficulty with entrainment.

Treatment of N24SWD depends on the underlying etiology. In blind individuals there is evidence that timed administration of melatonin (0.5mg) or more recently the melatonin agonist tasimelteon, ~1 hour prior to the desired sleep time can help to entrain the circadian clock. In sighted individuals treatment is more challenging, but typically involves allowing the individual to drift until they have reached their desired sleep time, then holding them in that window with a combination of melatonin (0.5 mg) prior to bedtime, and bright light on awakening (5).

Shift Work Disorder
Shift work disorder (SWD) develops in individuals who are required to work during times when they would normally be sleeping. It should be noted that not all individuals who are shift workers develop SWD. Symptoms include complaints of insomnia and/or excessive sleepiness. Symptoms should be present for at least 3 months. The diagnosis is confirmed with sleep logs and/or actigraphy that demonstrated a sleep-wake pattern that is disrupted by the required work schedule (1).

It is still not clear why not all individuals who are exposed to shift work develop symptoms. Some contributing factors include baseline chronotype, with morning-type individuals responding more poorly to night shifts than evening types. Other factors include the degree of social responsibilities that patients have during their off hours, which may interfere with their opportunity to sleep (11).

The treatment of SWD generally involves a multi-modal approach. During the work period, bright light and caffeine can be used to improve alertness. In addition, the stimulants modafinil and armodafinil are approved for use in treating sleepiness associated with SWD. During the sleep period, melatonin or short acting hypnotics can be used to help improve sleep quality. In addition behavioral interventions, including attempting to maintain a similar schedule on work and non-work days, and creating an environment conducive to sleep can also be beneficial (11).

Jet Lag Disorder
Jet lag disorder results from a mismatch between endogenous timing and the external environment, resulting from traveling across at least 2 time zones. Symptoms include insomnia, daytime sleepiness and/or gastrointestinal distress or other somatic symptoms (1).

The treatment of jet lag disorder depends on the direction of travel, the number of time zones crossed, and the duration of spent in the new time zone. If only traveling for <2 days, it may be easier to not try to adapt to the new time zone. For trips that are longer than 2 days, it is beneficial to try to reset the internal clock to adapt to the new time zone.

When traveling East the internal clock needs to advance, or move earlier. Typically on arriving at the new time zone it is best to avoid early morning light, and then seek out bright light in the afternoon. In addition, melatonin (2-5 mg) taken before bedtime can be helpful both to reset the clock and to help promote sleep.

When traveling West, the goal is to delay, or move the clock later. Generally the goal will again be to avoid morning light seek out bright light during the afternoon to help achieve this goal, but specific treatment times will need to be individualized, based on the number of time zones crossed (11).

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