# Circadian Rhythm Disorders in Children and Adults

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## 12.1 Circadian Rhythm Across the Life Span

Circadian rhythm, or the rhythm of life, is an essential element in the control of sleep wake cycles. The term circadian comes from the Latin words *circa* = about and *dien* = day. Circadian rhythms are endogenous rhythms lasting about 24 h or a day. These rhythms are seen in many aspects of human physiology, including daily rhythms in body temperature, in hormone production and secretion, and even in cardiovascular function and platelet function. However, the circadian rhythm seen in sleep wake cycles is the most distinctive and apparent to humans.

## 12.2 Influence of the Circadian Rhythm on Sleep

A person's circadian rhythms are determined by both genetic and environmental factors. The intrinsic circadian system acts like an alerting signal to promote wakefulness. The homeostatic drive, or sleep debt, is the other factor that influences sleepiness. The drive to sleep is the most when the homeostatic drive is the highest and the circadian system signal is the lowest. After a full sleep period, the

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A. Sharafkhaneh, D. Gozal (eds.), *Sleep Medicine*,
https://doi.org/10.1007/978-3-031-30010-3_12

homeostatic drive is the least. Combined with a high circadian alerting system level, this results in wakefulness and alertness. As the day progresses, the sleep debt, homeostatic drive, increases. With an overall high circadian alerting signal however, wakefulness continues. As evening approaches and light decreases, the circadian signal lessens. This combined with an exceedingly high sleep homeostatic drive results in the onset of sleep.

The intrinsic circadian sleep wake cycle in the absence of environmental cues is about 24.5 h. It needs to be modulated to match the earth's 24-h day-night cycle. This regulation, or entrainment as it is called, is determined by many cues. The cues to entrain systems to the circadian rhythm are also known as *zeitgebers* (German for time-giver). The biggest *zeitgeber* is the presence of light [1].

Light is detected by melanopsin containing photoreceptors located in the retina. These receptors are different from the rods and cones present in the retina that participate in the visual pathway. Signals from the melanopsin-containing photoreceptors travel through the specialized retinal projection system called the retinohypothalamic tract. Projections from this tract terminate on the suprachiasmatic nucleus (SCN), which is located above the optic chiasma in the hypothalamus. The inherent rhythm of the body and the SCN without the light input is about 24.5 h. With the light input, this rhythm is entrained to the 24-h cycle. The effect of light on the SCN is dependent on the phase of the circadian rhythm and time of day. Light has the biggest influence during changes from light to dark and vice versa.

In addition, fibers of the retinohypothalamic tract terminate to the thalamic intergeniculate leaflet (IGL). Projections from the IGL to the suprachiasmatic nucleus exist and are known as the geniculo-hypothalamic tract (GHT). GHT provides a secondary indirect pathway for the light cue to reach the SCN. IGL also plays a role in the entrainment of the circadian system by cues other than light.

SCN additionally receives signals from the median raphe nucleus of the midbrain directly and again indirectly through the IGL. These projections also participate in the mediation of non-light cues to the circadian system regulation.

The output pathways from the suprachiasmatic nucleus innervate target areas in the diencephalon and basal forebrain, which in turn target the circadian system messages to the sleep-wake systems, autonomic and neuroendocrine systems.

## 12.3 Circadian Rhythm Through the Life Span

Circadian rhythms start during early infancy. Sleep rhythms are irregular during infancy and slowly consolidate over time. The phase of sleep onset and waking is earlier during childhood than during adolescence. During adolescence and puberty, there is a biological drive toward phase shifting, leading to delayed sleep onset and wake times. Most adults have a usual phase sleep cycle. Older adults, however, tend to again revert to an early phase circadian rhythm, possibly due to ageing of the circadian system [2].

## 12.4 Pediatric Sleep and Rhythm

The circadian rhythm starts at early stages in fetal development. Between 6 and 18 weeks' gestation, the suprachiasmatic nucleus, which is the central controller of the circadian rhythm, develops. During the fetal period, the rhythms seen within the fetus include day-night rhythms in heart rate and respiratory rate and production of adrenal hormones. However, it is found that the rhythmicity of the fetus matches the mother's and so may be driven by the mother's rhythm rather than the fetus. By gestational age 18 weeks, melatonin and dopamine receptors are present in the fetal SCN, suggesting a role for these, being the cues for circadian information reaching the fetus [3, 4]. Additionally, the mother's core body temperature variations, eating schedule, and cortisol release circadian rhythms probably influence the fetus' rhythm [5].

After birth, full-term infants show little circadian rhythm immediately but develop day-night differences in activity within the first 2 weeks of life. It is during this time that the infant moves from responding to internal cues to external cues such as light [6]. During this time, rhythms in hormone production also start developing with the diurnal variation in cortisol levels apparent by 3–6 months of age. Melatonin production starts by 12 weeks of age, and over the next few months, consolidation of periods of rest and activity starts to develop [7]. Around this time, almost 70% of children sleep for about a 5-h stretch at night [8]. Between 3 and 6 months of age, the infant usually has three sleep periods with two short naps in the morning and afternoon and a longer sleep period at night.

Sleep during childhood continues to transition to more sleep consolidation to the nighttime. By about 2 years of age, the morning nap is transitioned out, and by age 6, most children stop daytime naps and sleep during the night.

## 12.5 Sleep During Adolescence

During adolescence, with the onset of puberty, circadian rhythms start to delay as seen by changes in the time of sleep onset that starts to occur later in the night and a phase delay in melatonin rhythm as well [9]. This phase delay is dependent on the presence of gonadal hormones [4]. There is also an increased sleep requirement and more daytime sleepiness. This is because the intrinsic period or circadian length of adolescents becomes longer, up to 25 h or longer (as opposed to 24.5 h in adults) [10]. Additionally, environmental factors, such as electronics usage, social pressures, and removal of parental oversight on bedtimes, result in changes in the sleep timings and duration. Electronics usage in particular plays a big role as the light exposure from the devices during the late evening and night times leads to a suppression of melatonin secretion in adolescents. The sensitivity of the circadian system to influences of light seems to be more prominent during the adolescent phase of life [11].

## 12.6 Sleep During Adulthood and Later Life

Between the ages of 20 and 50, adults gradually shift from the delayed phase of adolescence to an earlier circadian phase. During this time, sleep wake cycles are greatly affected by environmental cues such as work and social responsibilities [12]. Childcare responsibilities also impact the sleep cycle and phase of adults. Extrinsic circadian rhythm disorders during adulthood include shift work disorder and jet lag disorder. Shift work, where the timing of the work schedule occurs during habitual nighttime, has been associated with an increased risk of cancer, heart disease, and depression [13].

Older people tend to sleep less and have poor-quality sleep. The circadian sleep phase tends to advance further. This may be due to a decrease in melatonin levels. Endogenous body temperature nadirs also occur 2 h earlier than in younger adults [14].

## 12.7 Circadian Rhythm Disorders

Circadian rhythm sleep-wake disorders (CRSWD) are defined by the International Classification of Sleep Disoders-3 to have the following general criteria [15]:

1. A chronic or recurrent pattern of sleep-wake disruption related primarily to an alteration of the endogenous circadian timing system of a misalignment between the endogenous circadian rhythm and sleep-wake schedule desired or required by an individual's physical environment or social/work schedules.
2. The circadian rhythm disruption leads to excessive sleepiness, history of insomnia, or both.
3. Sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

Abnormalities in the circadian rhythm system at various levels can result in clinical disorders. Disorders of entrainment can occur if there is destruction of pathway bringing the light cue to the SCN. This can occur due to lesions in the retinohypothalamic tract or in the melanopsin-containing retinal cells. In blind persons with loss of rods and cones but intact melanopsin-containing cells, circadian rhythm entrainment persists. However, in those with complete destruction of the retina or the RHT tract, loss of entrainment results in a free-running circadian rhythm with a duration of about 24.5 h. This results in the sleep period being shifted by about 30 min each day. Problems with entrainment can also occur if individuals are exposed only to constant indoor lighting or darkness.

Damage to the SCN itself can also result in loss of a fixed circadian rhythm. These can be seen with anterior hypothalamus lesions or tumors.

The most common cause of circadian rhythm disorders is due to the endogenous clock or rhythm being out of sync with the external light-dark cycle. This can cause

the major sleep period to be prior to usual time of sleep based on light. This is known as advanced sleep phase disorder. Delayed sleep phase disorder occurs when the endogenous sleep phase occurs later than the usual sleep time. Extrinsic disorders of circadian phase occur due to asynchrony between the endogenous sleep wake cycle and external light dark timings due to travel (jet lag) or work schedules (shift work disorder).

Among children, the most common circadian rhythm disorders are delayed sleep phase disorder, free-running sleep phase disorder, or irregular sleep wake disorder.

## 12.8 Specific Circadian Rhythm Disorders

### Delayed Sleep Phase Disorder

This disorder occurs when the circadian-driven sleep cycle is delayed and the sleep onset is after the desired bedtime. Sleep complaints of sleep-onset insomnia can occur if the patient tries to go to bed at the desired bedtime but the circadian rhythm cycles is delayed beyond that. If the wake time is set by societal requirements (e.g., work or school), then the person can get inadequate sleep and have symptoms of daytime sleepiness.

In infants and children, delayed sleep phase disorder can occur due to a limit-setting disorder. Lack of parental limits on sleep time and wake time can result in children having a later sleep onset.

Delayed sleep phase disorder is the most common circadian rhythm disorder seen in adolescents. In a Norwegian study of 1285 high-school students between the ages of 16 and 19, 17.2% reported difficulty falling asleep before 2 am at least three nights a week, and 27.3% reported difficulty awakening at desired time. 8.4% reported both symptoms and met the researchers' criteria for delayed sleep phase [16]. Those who met this criteria showed lower-than-average school grades, higher levels of depression and anxiety, and increased usage of tobacco and alcohol. A study of sleep schedules and daytime functioning in 3120 adolescents showed that up to 87% of adolescents studied felt that they needed more sleep than they got. Most tended to delay their sleep onset and awakenings on the weekends as compared to school days. The delayed circadian phase that is commonly seen in adolescents combined with the need to awaken earlier than desired due to early school times led to decreased total sleep time [17].

### Advanced Sleep Phase Disorder

This disorder is seen when the circadian-driven sleep cycle is advanced such that sleep onset is before desired bedtime. The patient or parent can complain of early evening sleepiness prior to desired bedtime and also of early morning awakenings. Advanced sleep phase disorders are more common in the geriatric population. In children, the early morning awakening following an early bedtime occurs with

otherwise normal sleep quality and quantity. The consequences of ASPD are social if the child has to leave evening after-school activities early or is unable to complete homework.

### Irregular Sleep Phase Disorder

Irregular sleep-wake pattern consists of disorganized and variable times of sleep and wake. The total sleep time is normal, but it is broken up into multiple irregular bouts of sleep. This pattern is normal in newborns and infants up to age 6 months. Beyond this age, this sleep pattern is considered abnormal. In children, it is commonly associated with neurologic impairment. In the elderly, especially those with neurodegenerative disorders like Alzheimer's disease, this irregular sleep phase pattern can occur.

### Free-Running (Non-24 h) Sleep Wake Disorder

This disorder occurs when there is no entrainment to the light stimulus and 24-h cycle and is seen most commonly in blind people. The sleep-wake period is about 24.5 h without light entrainment, and therefore patients can have a shifting sleep schedule every day. A chronic pattern of delays in sleep onset and wake times can cause complaints of periodic insomnia followed by periodic excessive daytime sleepiness [18].

## 12.9 Circadian Rhythm Disorders in Neurodevelopmental Disorders

Circadian rhythm sleep disorders are seen in many neurodevelopmental disorders in children and adults. One of the most common neurodevelopmental disorders is ADHD (attention-deficit hyperactivity disorder). Children with ADHD report delays in sleep onset, eveningness preference, and poor sleep quality. They also show abnormal melatonin rhythms with phase delays and reduced amplitude [19]. Adults with ADHD can show delays in cortisol rhythm and decrease in the amplitude of their melatonin rhythms [20]. Sleep disorders are very common in children with autism spectrum disorders. Though a classic circadian rhythm disorder has not been defined in this subgroup of neurodevelopmental disorders, a decrease in evening melatonin levels has been found [21]. Administration of melatonin has been found to be helpful in treating children with ASD and sleep disturbances [22].

## 12.10 Circadian Rhythm Disorders in Neurodegenerative Disorders

Sleep disorders are more prevalent in elder individuals with neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD). Lower melatonin levels are seen as well as later sleep onset [23]. These sleep disorders may

precede other symptoms in PD and so may be a good early diagnostic finding. Sundowning is a common syndrome in patients with dementia in which increased restlessness, delirium, and agitation are seen in the early evening. Phase delay in sleep circadian cycles and decrease in body temperature rhythms correlate with the severity of sundowning symptoms [24].

## 12.11 Diagnostic Testing for Circadian Rhythm Disorders in Children and Adults

Detailed history taking is the most useful tool in determining if a circadian rhythm disorder is present. Details about sleep time and wake time, how long it takes to fall asleep, whether they are consistent or not, and how the pattern is on weekends and on holidays are useful questions to establish the pattern of sleep-wake cycle. If sleep patterns are irregular or out of sync with social and familial expectation, then a circadian rhythm disorder may be present [7].

A sleep log is helpful in determining the sleep schedule. Patients or caregivers are asked to record various parameters of sleep over a 2-week period, and this can be analyzed along with the sleep history to determine whether any circadian rhythm disorders are present.

Another diagnostic tool used to assess for circadian rhythm disorders is actigraphy. An actigraph is a watch-sized motion sensor usually worn on the wrist for a 2-week period. A sleep log is also kept by the patient during the same time. At the end of the recording, the data can be downloaded and analyzed to determine sleep onset time, wake time, time in bed, and duration of sleep. Actigraphy is recommended for use in both adults and children with circadian rhythm sleep wake disorders in the clinical guidelines for the use of actigraphy by the American Academy of Sleep Medicine [25]. Actigraphy is a useful tool especially in pediatrics to determine sleep patterns as children or adolescents may not be able to give a complete history or an accurate sleep log. Other diagnostic tests like polysomnogram (PSG) or MSLT (multiple sleep latency testing) are not required for the diagnosis of circadian rhythm disorders but may be useful in ruling out other sleep disorders.

## 12.12 Management of Circadian Rhythm Sleep Disorders in Children and Adults

The main management strategies in circadian rhythm sleep disorders include sleep hygiene, light therapy, melatonin therapy, and chronotherapy.

### Sleep Hygiene

Good sleep hygiene principles include regular bedtimes and wake times on all days of the week, regardless of social and work schedules. Even if the patient has to stay up late on a few nights, the wake time should remain the same.

## Light Therapy

Light therapy, or phototherapy, is the main management modality for DSPS in adults. Light has been long recognized to modulate circadian rhythm in humans [26]. The timing of administration of phototherapy is key to obtaining optimal therapeutic results. Light therapy administered after the temperature minimum ($T_{min}$), which is usually about 2 h before intrinsic habitual wake time, will result in a phase advancement of the circadian rhythm. If light therapy is administered before this $T_{min}$, then phase delay will occur.

## Melatonin and Agonists

Melatonin has been used widely in the treatment of circadian rhythm disorders and insomnia. Melatonin is an endogenous endolamine produced in the pineal gland from the amino acid tryptophan. The secretion is regulated by the suprachiasmatic nucleus. Melatonin secretion starts at the onset of dim light (dusk) and in proportion to the duration of darkness [27, 28]. Melatonin activates melatonin 1 (MT1) and melatonin 2 (MT2) receptors in the SCN. When melatonin is given therapeutically, it acts as a hypnotic agent [29]. It's role as a chronotherapeutic agent is debated. However, it is established that administration of melatonin at the same time every day can help entrain the circadian rhythm especially in free-running form [30]. Tasimelteon is a new MT1 and MT2 receptor agonist with more affinity for MT2 receptors than MT1 receptors and therefore useful in the treatment especially of non-24-h free-running disorder.

## Delayed Sleep Phase Syndrome

It is important to keep a set bedtime and wake time during all days of the week. Reverting to the intrinsic delayed sleep circadian rhythm on the weekends will cause the phase delay to persist. Avoiding electronics and bright lights in the evening is especially important in the treatment of this disorder. Bright lights from electronics can cause a further phase delay due to the response of the circadian system to light. Studies have shown that properly timed light therapy can cause a phase advance of circadian rhythm in patients with DSPS [31]. Light therapy should be administered in the mornings *after* the temperature nadir (Tmin). In order to clinically determine what the Tmin for the patient is, one would need to determine what the patient's intrinsic wake time is (e.g., what time the patient wakes on weekends or holidays without an alarm) [32]. Melatonin can be administered about 6 h before the desired time for sleep in both adults and children, with or without psychiatric comorbidities [32]. This causes a shifting of the endogenous melatonin secretion to an earlier time and helps with resetting the phase in DSPS. Chronotherapy, or progressively advancing sleep phase until desired sleep time is reached, may be useful for DSPS [33]. However, it is very

cumbersome for the patients to follow this therapy, which is required to be done over a few weeks.

### Advanced Sleep Phase Syndrome

Treatment of advanced sleep phase syndrome is similar to that of DSPS but in the opposite time of administration of therapies. The child or adult with ASPS should be exposed to light therapy in the evenings, and melatonin administration should be early morning. In the morning, the room should be kept dark. Exercise in the evening can also be recommended.

### Irregular Sleep-Wake Rhythm (ISWR)

In the treatment of ISWR, daytime bright light exposure may help. Multiple studies have shown a positive benefit of bright light exposure in nursing home patients with dementia [33]. The best management strategy for these patients, however, is a mixed modality strategy incorporating bright light exposure along with physical activity and other behavioral elements. Melatonin is *not* indicated for the treatment of ISWR in elderly patients with dementia but may be useful in treating children with ISWR and severe psychomotor retardation. Mixed modality therapy may also be useful for these children [33].

### Free-Running (Non-24 h) Disorder (FRD)

As in the other circadian rhythm disorders, keeping a regular bedtime and waketime schedule is important in the management of this disorder. Morning light therapy may be useful to entrain sighted patients with FRD. In blind individuals, the use of external cues, other than light, are key for the patient to determine the time of day. Therefore, a regular schedule during the day, consisting of exercise, fixed mealtimes, and social activities, is useful to prevent napping during the day. Melatonin (commonly 3 mg dose) administered 1 h before desired bedtime is useful in establishing a regular sleep-wake schedule in sighted patients as well as blind patients with FRD [34, 35]. Tasimelteon, a potent dual-melatonin receptor agonist, has been the only FDA-approved drug for use in the treatment of free-running disorder [36].

## 12.13 Conclusion

Circadian rhythms are endogenous biological rhythms that last around 24 h and exist in all living organisms. The circadian rhythm starts to develop during the fetal period, and its physiology changes through an individual's life span. When there is a misalignment of a person's endogenous circadian rhythm with the desired

sleep-wake schedule, circadian rhythm sleep disorders emerge and can cause daytime sleepiness or insomnia. Circadian rhythm sleep disorders are common both in the pediatric age group and in adults and in the geriatric age group. The type of disorder, however, can vary with age. Additionally, what is normal sleep pattern at one age can be a disorder at another age, e.g., an irregular sleep-wake rhythm is normal in infants but abnormal when seen in older children and older adults. Similarly, a delayed sleep phase circadian rhythm is normal in most adolescents but can cause problems in adults. Advanced sleep circadian phase is seen normally in children but can be a disorder in older adults. The management of these disorders also varies from the pediatric age to adults to elderly. Transitioning care of patients from pediatric to adult medicine requires a good understanding of the normal circadian physiology and the various circadian sleep disorders.

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