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Review Article

Sleep-Wake Cycles: Revealing the Hormonal Symphony of Melatonin and Circadian Rhythm Disorders - A Comprehensive Review

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ABSTRACT

Circadian rhythm (biological rhythm) disorders alter the body's natural sleep-wake cycles and have been associated with mood fluctuations, cardiovascular problems and cognitive degeneration. Notable disorders that result from an imbalance between an individual's internal circadian rhythms and external factors, such as light exposure and social responsibilities, can lead to conditions like delayed sleep-wake phase disorder (DSPD), advanced sleep phase syndrome (ASPD) and shift work disorder (SWSD). The pineal gland secretes melatonin, a hormone that promotes sleep and indicates darkness, to stabilize the circadian rhythms. This study explores the impact of melatonin on the suprachiasmatic nucleus (SCN), the brain's central clock, and its potential therapeutic applications for disorders that disrupt the circadian rhythm. Melatonin treatment lowers sleep onset latency (SOL), advances sleep-wake cycles in individuals with DSPD, and enhances morning alertness, according to clinical investigations. It improves the quality of sleep, which has some advantages for ASPD, especially in older persons. Melatonin lessens daytime drowsiness, eases insomnia, and helps sleep patterns adapt to work schedules for SWSD. In addition to discussing ideal dosage, possible adverse effects, and the necessity of customized care, this review highlights the significance of more research on the long-term safety of melatonin, medication interactions, and its application in combination therapy for disorders of the circadian rhythm.

INTRODUCTION TO CIRCADIAN RHYTHM (BIOLOGICAL RHYTHM)

The 24-hour cycle of biological activity is known as the circadian rhythm, or biological rhythm. They play a crucial role in regulating body temperature, sleep-wake cycles, hormone synthesis, and other physiological processes. The hypothalamic suprachiasmatic nucleus (SCN) serves as the master clock that synchronizes the body's internal processes with external events. It is in charge of establishing these rhythms.^[1] The SCN receives direct inputs from light-sensitive retinal ganglion cells, which aid in coordinating the biological rhythm—also referred to as

the circadian rhythm—with the outside day-night cycle.^[2] light is the most potent environmental component influencing circadian rhythms. The SCN uses information about the time of day from the daily light-dark cycle to coordinate various physiological rhythms and control the pineal gland's synthesis of melatonin. When circadian cycles align with these environmental cues, it improve metabolic functions, sleep patterns, and overall health.^[3] Moreover, circadian rhythm disturbances can lead to a range of illnesses known as circadian rhythm disorders (CRDs), which mainly impair sleep but may also have more extensive detrimental effects on general health.^[4]

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Molecular Mechanisms of Circadian Rhythm (Biological rhythm)

Endogenous, self-sustaining oscillations known as biological rhythms control a number of physiological functions throughout the course of around twenty-four hours. These cycles, which are influenced by environmental factors including light, temperature, and social interactions, are managed by the SCN. The feedback loop of clock genes, including as CLOCK, BMAL1, PER, and CRY, forms the molecular foundation of biological cycles. These genes establish periodic patterns of gene expression that control daily cycles in behavior and physiology.^[3]

Peripheral clocks in other tissues and organs, in addition to the SCN, also adhere to circadian rhythms; nevertheless, the SCN synchronizes them to maintain temporal coherence across the body.^[1] For instance, the heart's circadian clock synchronizes heart rhythms with daily activity patterns, whereas the liver's circadian clock controls metabolic processes in accordance with food schedules.^[5] When these circadian rhythms are in synchronise with external time signals, including the light-dark cycle, people have regular cycles of sleep and wakefulness, as well as strong cognitive performance and overall health.

Disorders of the Circadian Rhythm (Biological rhythm)

When the body's internal physiological clock is not in sync with external stimuli, it can lead to circadian rhythm disorders, which can disrupt the cycle of sleep and wakefulness and other circadian-regulated activities. These illnesses are classified according to the type of misalignment.

A significant change in the primary sleep period's schedule that causes it to occur later than the person's chosen or socially acceptable sleep hour is the hallmark of delayed sleep-wake phase disorder (DSPD). People with DSPD wake up much later than they would want to because they struggle to fall asleep at a regular time. This mismatch can cause significant pain and disruptions to day-to-day functioning, especially in professional or educational environments. Young adults and adolescents, who comprise around 7 to 16% of the population, are thought to account for the bulk of DSPD cases.^[6]

Because of their faster sleep-wake cycle, people with advanced sleep phase type (ASPD) go to bed and wake up several hours sooner than they would like to. Early morning awakenings and early evening fatigue are more common in older adults with this condition. In the evening, social activities may be disrupted and sleep loss may result when individuals with ASPD attempt to stay up later than they typically would.^[2]

Those with irregular work schedules, such as night or rotating shifts, are more susceptible to inconsistent sleep-wake syndrome (SWSD). When a person's work schedule and their natural circadian rhythm are out of

sync, it can be difficult for them to fall asleep, stay asleep, and wake up without feeling too exhausted. Prolonged sleep deprivation and circadian disturbance are common causes of SWSD, which is linked to an increased risk of cardiovascular disease, metabolic diseases, and cognitive impairment.^[7]

Non-24-hour sleep-wake disorder (N24) is more common in those with visual impairments. Their internal clock "free-runs," frequently lasting a little more than 24 hours, when light cues that aid in regulating circadian rhythms are absent, resulting in a progressive alteration of the sleep-wake cycle. Excessive daytime sluggishness and sleeplessness result from the internal clock becoming more out of sync with the 24-hour day.^[8]

The absence of a consistent circadian rhythm, which results in several short sleep periods spread out over a 24-hour period rather than a single, unbroken night of sleep, is the hallmark of the rare illness known as irregular sleep-wake rhythm disorder. Individuals who suffer from this illness frequently struggle to have a regular wake-sleep pattern and experience significant sleep fragmentation.^[6]

Health Implications of Circadian Rhythm (Biological rhythm) Disorders

Circadian rhythm issues have a major effect on overall health in addition to sleep. Numerous health issues, including obesity, heart disease, metabolic syndrome, and mental diseases like anxiety and depression, can be brought on by a prolonged disturbance of the circadian rhythm.^[7] Furthermore, there is proof that irregularities in the circadian rhythm are linked to compromised immune systems, elevated inflammatory reactions, and a higher chance of developing chronic diseases like cancer.^[9] The combined effects of sleep deprivation, circadian misalignment, and lifestyle factors, including poor diet and reduced physical activity, for example, are more likely to affect shift workers with SWSD and raise their risk of type 2 diabetes and cardiovascular disease.^[7] Another problem that patients with ASPD or DSPD may have is chronic sleep deprivation. This can lead to a decline in quality of life, emotional control, and cognitive function.^[6]

Since circadian rhythm issues have a major detrimental impact on health, more and more individuals are interested in developing effective treatment solutions. Melatonin is one hormone that is crucial for regulating circadian rhythms and might be utilized to address these issues. Melatonin therapy at the appropriate time can alter circadian cycles and reduce symptoms of disorders such as DSPD and SWSD.^[9]

Delayed Sleep-wake Phase Disorder (DSPD)

A persistent delay in the sleep-wake cycle, frequently lasting longer than two hours after the usual or preferred bedtimes and waking times, is a hallmark of DSPD. In general, people with DSPD sleep late, occasionally early, and wake up later in the day. It becomes more challenging

to finish daily duties like work, school, or social events when one's sleep schedule deviates from the norm. Reduced functionality throughout the day is the result of chronic sleep deprivation.^[10]

According to estimations, DSPD is more common among young adults and teenagers (7–16% in this age range).^[6] Around puberty, when circadian timing changes naturally make it more difficult to go to bed early, DSPD frequently starts. In contrast to occasional late nights, DSPD is a chronic illness that can last for months or even years and cause significant suffering. People with DSPD often describe symptoms of insomnia, including difficulty falling asleep at the right time and excessive daytime tiredness caused by inadequate sleep duration.^[11]

Instead, then having trouble falling asleep, DSPD is characterized by a disruption of the internal circadian rhythm with external time cues, unlike other sleep disorders including insomnia or hypersomnia. Risk factors associated with the condition include irregular sleep-wake cycles, inadequate exposure to early light, and a hereditary predisposition.^[10] Effective treatment techniques, especially those that seek to realign the circadian rhythm with the ideal sleep-wake cycle, depend on an understanding of the basic causes and characteristics of DSPD.

Melatonin supplementation for DSPD

The pineal gland produces the hormone melatonin, which is essential for regulating the sleep-wake cycle since it signals the beginning of night and promotes feelings of fatigue. One of the things that causes people with DSPD to sleep later is their delayed melatonin synthesis. For those with DSPD, melatonin therapy has emerged as a potentially helpful therapeutic strategy to encourage the sleep phase. It is feasible to change the commencement of melatonin production earlier in the evening by giving melatonin exogenously. This would allow for an earlier bedtime and bring the sleep-wake cycle into line with societal expectations.

Melatonin Treatment for DSPD

In a thorough systematic study published in Sleep Medicine Reviews, Micic (2017) assessed how well melatonin therapy worked to control the sleep-wake cycle in people with DSPD. When administered at the appropriate time, melatonin supplementation can promote the sleep phase and lessen sleep onset delay, according to the research, which summarized the findings of many RCTs and observational studies.^[11]

This review emphasized that melatonin's efficacy depends on when it is administered. When consuming melatonin, it is best to do so two to three hours before the planned bedtime. This allows the exogenous melatonin peak to coincide with the person's natural circadian cycle. According to Micic (2017), the study also mentioned that there are differences in the melatonin dosage: lesser

dosages (0.3–0.5 mg) are frequently enough to cause the desired phase shift (Table 1), but greater doses may result in extended melatonin levels and possible side effects in the morning.^[11]

Effects of melatonin on sleep phase delay in adolescents with DSPD

Burgess conducted another significant study that looked at how melatonin affected the sleep phase delay in teenagers with DSPD. (2017). The Journal of Clinical Sleep Medicine published it. Due to the typical changes in circadian timing that come with puberty, teens in the study were more susceptible to DSPD. Following overnight melatonin injections, the researchers tracked changes in sleep quality, sleep onset latency, and the whole circadian phase over many weeks.^[12] The findings demonstrated that melatonin improved the quality of participants' sleep by considerably reducing the time it took for them to fall asleep. The study also discovered that melatonin therapy advanced the circadian rhythm, bringing the sleep-wake cycle closer to the intended timetable. The authors emphasized that in addition to melatonin, other treatments, such exposure to morning light and other sleep hygiene habits, are required to maintain the long-term benefits of melatonin therapy.^[12]

Advanced Sleep Phase Syndrome

A circadian rhythm abnormality known as advanced sleep phase abnormality (ASPD) results in a markedly earlier than normal sleep-wake cycle transition. Individuals with ASPD typically go to bed and wake up many hours earlier than is customary or socially acceptable. For example, a person with ASPD could frequently wake up around two in the morning and feel drowsy at six in the evening. Social and professional functioning might occasionally be seriously hindered since this enhanced time is out of pace with the demands of modern life.^[13]

Although it may happen at any age, elderly folks are the ones who experience ASPD the most. As people age, their circadian rhythms usually alter, which might be the cause of the rise in ASPD cases. The exact cause of Advanced Sleep Phase Syndrome (ASPD) is unknown however genetic factors are believed to play a significant role. The discovery has suggested a possible genetic component that some individuals with ASPD had mutations in genes that control the circadian rhythm, such as PER2 and CK1 δ .^[14] The difficulty in remaining awake or aware in the evening, which results in early bedtimes and early morning awakenings, is the main symptom of ASPD. This imbalance sometimes makes it difficult for the individual to maintain a normal social life and may make it difficult for them to participate in nocturnal activities. Additionally, those who attempt to adhere to a more conventional sleep schedule may experience sleep deprivation, which might lead to fatigue during the day and compromised cognitive abilities.^[15]



Table 1: Summary of melatonin studies for DSPD

Study	Sample size	Melatonin dose	Administration time	Findings
Micic (2017)	30	0.3–0.5 mg	2–3 hours before bed	Reduced sleep onset latency, advanced sleep phase
Burgess JR (2017)	50	0.3–0.5 mg	2 hours prior to going to bed	decreased sleep start delay and increased sleep quality

Melatonin Supplementation for ASPD

Advanced sleep phase syndrome (ASPD) can be treated with melatonin, which controls the sleep-wake cycle. It does not effectively cure other abnormalities of the circadian rhythm, such as delayed sleep-wake phase disorder (DSPD). Melatonin may not be enough to completely move the advanced sleep phase to a later period, despite some research suggesting that it can somewhat improve the duration and quality of sleep in those with ASPD.

Melatonin in ASPD

In a review published in *Sleep Medicine* in 2016, Chung *et al.* looked at how well melatonin supplements worked in treating ASPD. The study compiled results from several research studies that examined melatonin use in people with ASPD, with an emphasis on how it can postpone the beginning of sleep and enhance the standard of sleep.^[16] The study came to the conclusion that while melatonin can increase the quantity and quality of sleep, there isn't much proof that it can significantly postpone the sleep phases of people with ASPD (Table 2). The results suggested that the advanced phase shift observed in ASPD may not be entirely reversible with melatonin alone. The modest improvements shown in some trials imply that melatonin could be more effective when combined with other therapeutic modalities, such as bright light therapy at night or behavioral modifications that delay sleep.^[16]

Melatonin for ASPD in elderly patients

Results of a research on the effects of melatonin supplementation in older persons with ASPD that was carried out by Figueiro (2016). This result is particularly relevant since older adults with ASPD are more prone to spontaneously shift to earlier sleep and waking hours^[17]. Researchers noticed changes in the length, quality, and commencement of sleep in a sample of older people with ASPD after administering melatonin. The results demonstrated that melatonin administration increased the sample's sleep duration and quality. However, the benefits were less pronounced when compared to other circadian rhythm disorders, including DSPD and SWSD. Even while melatonin improved some people's sleep, the researchers discovered that it did not completely reverse the advanced phase shift. This suggests that in order to produce a more noticeable sleep-wake cycle delay, further treatments would be required.^[17]

The inability to change the advanced phase of these people's circadian clocks may be the reason for melatonin's

low efficacy in treating ASPD. When paired with melatonin, bright light treatment in the evening, which aids in delaying the circadian phase, could provide a more successful strategy. Further aiding in the modification of the sleep phase includes preserving regular sleep-wake cycles and shielding individuals with ASPD from early morning light exposure.

Shift Work Disorder

A circadian rhythm condition known as shift work disorder affects people who work erratic schedules, such as night, rotating, or evening shifts. This disorder causes disturbed sleep patterns and possible health problems by causing a mismatch between an individual's internal biological clock and their external surroundings.

People with SWSD experience a discrepancy between their work schedule and their internal circadian rhythm. These irregular work hours throw off the internal clock, which typically operates on a 24-hour cycle. This misalignment makes it difficult to get to sleep, stay asleep, and get up at the appropriate time.^[18] Usually resulting in insufficient and fragmented sleep, this misalignment aggravates chronic sleep deprivation.

The effects of SWSD are not limited to sleep disruption. People with SWSD frequently experience exhaustion, excessive daytime drowsiness, insomnia, and cognitive impairment. Chronic sleep deprivation linked to SWSD is linked to a number of health problems, including metabolic syndrome, cardiovascular disease, gastrointestinal disorders, and compromised immune function.^[19,20]

SWSD has a major effect on the social and professional spheres. Relationship management, everyday chores, and work performance can all suffer from irregular sleep patterns. This mismatch may lead to psychological stress and negatively impact overall quality of life, as stated by Drake (2004).^[21]

Melatonin supplementation for SWSD

Supplementing with melatonin has shown promise in treating SWSD, primarily by helping to adjust the sleep-wake cycle to accommodate irregular work patterns. Numerous studies have examined how effective melatonin is in reducing SWSD symptoms and improving overall sleep quality.

Treatment of SWSD with Melatonin

Liu (2018) assessed the efficacy of melatonin supplementation in treating SWSD in a thorough

Table 2: Summary of melatonin studies for ASPD

Study	Sample size	Melatonin dose	Administration time	Findings
Chung (2016)	25	1-3 mg	1 hour before sleep	Limited efficacy in delaying sleep phase
Figueiro MG (2017)	20	1-2 mg	1 hour before sleep	Improved sleep duration and quality

investigation and meta-analysis that was published in Sleep Medicine Reviews. The study compiled the findings of other investigations assessing the effects of melatonin on the quality of sleep and symptoms associated with SWSD.^[22]

According to the research, using melatonin supplements at the suggested time of sleep beginning can enhance sleep quality and lessen SWSD symptoms. It has been demonstrated that melatonin works best when taken one to two hours prior to the scheduled bedtime. According to the meta-analysis, shift workers who took melatonin saw notable improvements in their overall sleep duration, sleep efficiency, and sleep start latency. Melatonin may be a useful therapy for SWSD, enhancing sleep quality and lowering tiredness in shift workers, according to Liu (2018).^[22]

Melatonin's efficacy in treating SWSD

In a randomized controlled experiment (RCT) published in Occupational Medicine, McGowan (2017) assessed the effectiveness of melatonin in treating SWSD. In shift workers with sleep issues, the effects of melatonin on sleep metrics and daytime functioning were evaluated.^[23] According to the study, melatonin treatment considerably lessened the sleep disturbances brought on by working shifts. The participants reported less daytime weariness, better sleep quality, and shorter sleep latency. Additionally, melatonin has been shown to improve concentration and lessen general weariness. According to McGowan (2017), melatonin is a helpful and successful therapy option for those with SWSD, lessening the detrimental effects of irregular work patterns on sleep and daytime functioning.^[23]

By encouraging sleep onset and re-establishing regular rhythms, melatonin is a flexible and efficient treatment for circadian rhythm disorders (Fig. 1). It helps people with DSPD to synchronize their sleep-wake cycles with typical social hours, improving sleep quality and day-to-day functioning. Melatonin greatly improves the quality

of sleep, but it might not completely cure advanced phase shifts in ASPD. This suggests that a mix of treatments, such as behavioral interventions and light therapy, may be necessary for the best possible care. Melatonin helps people with SWSD adapt to their unpredictable work schedules by lowering excessive daytime weariness, enhancing overall sleep quality, and encouraging better internal clock synchronization with work hours. Melatonin has a favorable safety profile when compared to traditional sleep aids, which have dangers, including reliance and cognitive impairment. Because of its low side effects and ability to regulate the circadian cycle, it is a useful chronobiotic in therapeutic practice. Future studies should focus on evaluating long-term effects, optimizing dosage schedules, and exploring integration with other therapies, such as light therapy or cognitive-behavioral approaches. If melatonin regimens are tailored to each patient's metabolic profile and circadian rhythms, melatonin may be a safe and effective alternative for treating abnormal

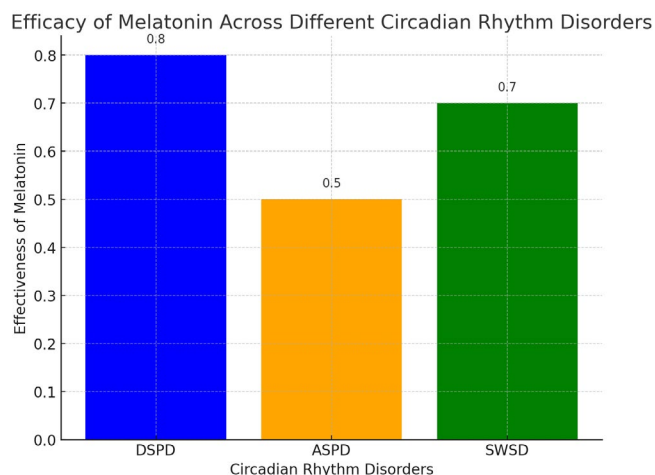


Fig. 1: Evaluating melatonin's efficacy in treating ASPD, SWSD, and DSPD in light of several research. The graph indicates that the efficiency of melatonin varies depending on the disease.

Table 3: Summary of melatonin studies for SWSD

Study	Sample size	Melatonin dose	Administration time	Findings
Liu (2018)	40	2 mg	1-2 hours before sleep	Enhanced sleep quality and decreased daytime sleepiness.
McGowan AE (2017)	35	1-3 mg	1-2 hours before sleep	Alleviated sleep disturbances, reduced daytime sleepiness



circadian rhythms. More in-depth research is anticipated to validate the significance of melatonin in sleep medicine and circadian health management.

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