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Circadian Rhythms and Insomnia – Approaching the Time Barrier

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Circadian rhythm disorders can occur either as the result of an externally imposed shifted sleep schedule (eg, shift work and rapid travel across time zones) or because of an intrinsic individual tendency to sleep at unusual times. Conditions such as delayed, advanced, or non-24-hour sleep-wake disorders have an intrinsic etiology, often aggravated by the patient's sleep behaviour. There is sufficient evidence to support a role for circadian factors in the pathophysiology of chronic insomnia, although patients with chronic sleep onset and sleep maintenance difficulties are generally unaware of their rhythms abnormalities. This issue of *Insomnia Rounds* reviews the main circadian rhythm disorders, addresses the role of circadian rhythms in the etiology of chronic insomnia, and clarifies how this knowledge can improve the treatment of insomniac patients.

What are Circadian Rhythms?

Circadian rhythms are rhythms of about 24 hours (from the Latin *circa*, meaning "about", and *dies*, meaning "day") and have been observed in humans for most physiological and behavioural measures, including hormone secretion, sleep propensity and architecture, subjective mood, alertness and performance levels. These rhythms are self-sustained and generated by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, considered to be the master circadian clock. The SCN circadian clock comprises a population of coupled "clock" cells with the intrinsic capacity to generate a rhythm in firing activity with a ~24-hour periodicity. Indeed, negative and positive feedback loops regulate the expression of a set of clock genes that are activated or repressed by their own protein products. Clock genes also drive circadian cycles locally in other brain regions and many peripheral tissues, including skin, adipose tissue, oral mucosa, peripheral blood mononuclear cells (PBMCs), bone marrow, colon cells, and hair follicles.[1,2] Clocks in these tissues normally rely on timing signals from the SCN to maintain appropriate internal synchrony. Oscillations generated by clock genes regulate expression of clock-controlled genes which ultimately leads to rhythms in tissue functions.

Circadian rhythms are self-sustained and persist in constant time-free conditions. When free to run without the influence of environmental synchronizers, endogenous circadian rhythms adopt a period that is close to, but slightly different from, 24 hours. In humans, the circadian period varies from 23.5 to 24.5 hours and is slightly shorter in women than in men[3] (24.09±0.2 hours versus 24.19±0.2 hours). This 6-minute difference appears sufficient to advance the temperature and melatonin phase relative to wake time (ie, phase angle) 22 and 28 minutes earlier, respectively, in women compared to men. These sex differences in circadian physiology may contribute to the increased sleep complaints observed in women.

How are Circadian Rhythms Set for Daily Living?

In real life, an individual living on a day-oriented schedule will adopt a 24-hour rhythm and adapt to the terrestrial environment. This is achieved by a process called circadian entrainment by which environmental synchronizers adjust the circadian system to the environment. The light-dark cycle is the most powerful environmental synchronizer for most animals

including humans. Photic stimuli are transduced by the retina and information is transmitted to the SCN via the retinohypothalamic tract, a direct monosynaptic pathway.

A population of retinal ganglion cells containing the photopigment melanopsin mediates entrainment of the circadian system by light, although retinal rods and cones can play a role. Exposure to light can shift rhythms of the central clock and peripheral clocks by an amount and direction that depends on the circadian phase at which light exposure occurs.[4,5] Consequently, the pattern of light exposure can be timed to facilitate resetting of the circadian system in any desired direction. Exposure to light in the late evening/early night will delay rhythms to later times (akin to westward travel) whereas light exposure in the late night/early morning will advance rhythms to earlier times (akin to eastward travel).[5] A practical rule of thumb is that light before the nocturnal body temperature minimum (which occurs about 1–2 hours before habitual wake-up time) will phase delay the circadian clock, light after the temperature minimum will phase advance the clock, and light from late morning to early evening will have little effect.

Light intensity, its spectral composition, and prior exposure to light influence the resetting response of the circadian system. Light in the blue visible range of 440–480 nm induces larger phase shifts than white light;[6] however, a switch of sensitivity towards light in the green visible range of 555 nm was observed at lower irradiances.[7] The central circadian clock is sensitive to low indoor room light,[8] and integrates light information in such a way that its effect can be sustained even when light is intermittently interrupted by darkness.[9]

What factors other than light influence circadian rhythms?

Administration of melatonin in the evening and morning can advance and delay endogenous circadian rhythms, respectively.[10] Other non-photic synchronizers such as exercise and the timing of food availability can shift and entrain circadian rhythms in various animal models, but effects of these stimuli in humans are not as well studied, and appear to be weak, as indicated by the failure of the circadian clock in several totally blind people to entrain to local time despite living on a 24-hour day.[11]

How Does the Circadian System Affect Sleep?

The quality and duration of sleep depends on a complex interaction of homeostatic and circadian processes. Sleep homeostatis refers to the progressive increase of sleepiness, and subsequent sleep intensity that occurs in proportion to the duration of wake-time. Sleep intensity is mainly quantified by the amount of deep sleep or slow wave sleep (SWS, Stages 3-4 as defined by Rechtschaffen and Kales,[12] and stage N3 in the new American Academy of Sleep Medicine scoring sleep staging system[13]) and electroencephalographic slow wave activity (SWA) in a given sleep period.[14] Homeostatic properties of sleep are thought to reflect a recovery process that occurs during sleep to maintain or restore normal vigilance levels at wake time.

Two high and 2 low sleep propensity zones occur during the 24-hour day.[15] A first high sleep propensity zone is observed at the end of the night, near the core body temperature minimum, and a second in the early afternoon. These two zones can explain the increased sleepiness and accident risk in the late night as well as the post-lunch dip in alertness. Evening and morning "wake-maintenance zones" (WMZ) have been described during which sleep initiation is difficult. The evening WMZ is observed 1–2 hours prior to the regular bedtime and the morning WMZ is observed 3–4 hours after awakening. Under normally entrained conditions, sleep is initiated on the declining limb of the core body temperature cycle, 1–2 hours after the evening WMZ. At bedtime, it has been proposed that melatonin secretion is involved in a cascade of events leading to increased distal thermal loss and sleep promotion.[16] In conditions where the endogenous circadian system is delayed relative to the sleep schedule (eg, after travel 1–3 time zones east), the evening WMZ might coincide with bedtime, a situation which can cause substantial sleep onset difficulties.

Sleep latency, sleep efficiency, the proportion of rapid eye movement (REM) sleep, REM sleep latency, and the fraction of sigma activity (12–15 Hz; ie, sleep spindles) in non-REM sleep all vary throughout the circadian day.[17] Studies indicate that the circadian phase at which sleep is initiated significantly affects the ability to fall asleep and the quality and duration of the subsequent sleep period.

How to Deal With Sleep Disturbances in Night Shift Work

People sleep and perform better when they maintain a nocturnal sleep schedule. Night work creates a mismatch between the circadian clock and the sleep/wake schedule.[18] This mismatch and the resulting sleep and wake disturbances increase the risk of accidents as well as of developing several medical conditions such as cardiovascular and gastrointestinal diseases, various types of cancer, and psychological disorders.[18]

Is insomnia more common in shift workers?

Complaints of insomnia symptoms are common among night shift workers.[19] In a study of more than 2500 workers aged 18–65 years, symptoms of insomnia or severe drowsiness meeting diagnostic criteria for shift work sleep-wake disorder were observed in 32.1% of night workers and 26.1 % of workers on rotating shifts compared to 18.0% of day workers.[20] Evaluation by polysomnographic (PSG) sleep recordings usually reveals that the average daytime sleep duration is shortened by 1–4 hours compared to nighttime sleep, resulting in

a need for recovery and a 8%–43% increase in nocturnal sleep duration on days off.[19] For most shift workers, entrainment to their atypical work schedule remains incomplete as they continue to be exposed to environmental synchronizers, especially morning light, that impede circadian clock adjustment. In most individuals, circadian misalignment of the cortisol and melatonin rhythms to the shifted sleep/wake schedule persists despite consecutive shifts worked.[18]

How can sleep be improved with shift work?

A variety of countermeasures have been proposed to reduce the fatigue of shift workers including some that are intended to improve circadian adaptation to night schedules.[18] Our group has studied manipulation of the light-dark cycle to which nurses and police officers working nights are exposed.[19,21-23] Exposure to phototherapy lamps during the first 6 hours of night shifts, dark goggles in the morning and maintenance of a regular daytime sleep schedule produced a complete entrainment of the core body temperature, salivary melatonin, and cortisol rhythms to night shift work in permanent night nurses,[19,21] accompanied by a lengthening of the daytime sleep period compared to control nurses.[19] Wearing orange-tinted goggles in the morning permitted partial entrainment of circadian rhythms of police officers and stabilized their psychomotor performance throughout 7 consecutive night shifts.[22] Police officers who demonstrated circadian entrainment to night shift work exhibited levels of alertness and performance during wake periods as well as sleep duration and quality during rest periods similar to those on day shifts.[23] They also showed favourable indices of heart rate variability compared to unadapted officers.

Spontaneous circadian adaptation, or adaptation with the help of bright light and/or goggles, is effective to improve alertness, performance, and sleep of night shift workers. This approach has the disadvantage of disturbing circadian adaptation during rest days, as most workers return to a day-oriented schedule. A proposed alternative is to shift the circadian system just enough to delay the circadian nadir of alertness, which normally occurs at the end of the night, by a few hours such that it occurs after the work shift during daytime sleep.[24] This approach reduces the performance deficits at the end of the night, facilitates sleep onset in the morning, and eases the transitions between days on and days off.

It is thus feasible to design interventions that improve circadian adaptation to night shift work. However, such interventions do not appear advantageous for irregular work or rapidly rotating schedules.

Can melatonin reset circadian rhythms or improve sleep in night workers?

Exogenous melatonin is known to have sleep-promoting and circadian phase shifting (chronobiotic) effects. Sustained-release melatonin (1.8 mg) administered for 2 days before daytime sleep in simulated night shift work improved total sleep time and sleep efficiency compared to placebo, although for only 1 day.[25] This effect was more pronounced in participants with sleep difficulties and no alertness impairment was observed during the wake period. Increased daytime sleep duration without alertness impairment was also reported with melatonin 6 mg administered at 9 am for 2 days.[26] Melatonin (0.5 mg or 3.0 mg) produced partial dose-dependent circadian phase advances and increased daytime sleep in participants who slept in the evening prior to a simulated night shift.[27] The use of melatonin tablets or melatoninergic receptor agonists can be beneficial for shift workers, although further large scale experimental testing is needed to support their clinical efficacy.

Adjusting to Jet Lag

Rapid travel across ≥2 time zones induces an abrupt desynchrony between circadian clocks and the new sleep schedule at destination. About two thirds of transmeridian travelers present with acute symptoms of sleep disturbances, fatigue, impaired alertness and performance, gastrointestinal malaises, headaches, and irritability.[28] Rhythms linked to the sleep–wake cycle (eg, secretion of growth hormone and prolactin) adjust more rapidly to the new time zone than those more tightly coupled to the circadian system (eg, secretion of cortisol and melatonin).[29] On average, the circadian system takes about a day to adjust to each time zone crossed; for most people the adjustment is faster for westward trips and during the first days following arrival in the new time zone.[28]

Eastward flights involving approximately 6 hours of time zone changes lead to sleep onset difficulties, more awakenings in the first hours of sleep, prolonged time to the onset of REM sleep, reduced REM sleep duration, and early morning sleepiness. In comparison, westward flights across similar distances lead to more awakenings in the last hours of sleep, foreshortened REM sleep onset, and evening sleepiness. Sleep disruption will be more severe on the second day after arrival whereas deep sleep is often increased on the date of arrival due to recovery from the acute sleep debt. Substantial individual variability exists in tolerance to jet lag and can be affected by age, sleeping behaviour, and exposure to light and darkness.[9]

What strategies can be used to adjust to jet lag?

For short (≤2 days) trips, it is advised to keep a sleep schedule as close as possible to the departure time zone in order to limit sleep/wake disruption upon return home. Get as much sleep as possible by taking advantage of the circadian variation of sleep propensity, the use of aids such as earplugs, eyeshades, neck support, or even a mild hyp-

notic drug in the plane, and avoiding excessive consumption of alcohol and caffeinated beverages. For longer trips, sleep hygiene measures should be implemented to hasten circadian entrainment to the new time zone.[28] A regular schedule of exposure to light and darkness, meals timing, physical activities, and social interactions is suggested. For trips within 6 time zones, adopt a rest-activity pattern that fits the destination as soon as possible. Light exposure in the late afternoon/early evening should be favoured for westward trips. For eastward trips, light exposure is preferable in the afternoon in the first days after arrival, followed by morning/early afternoon light exposure a few days after arrival. Preparation for the new sleep schedule can also be started prior to departure, by slowly and partially adjusting the sleep schedule to the destination schedule, although this is not commonly done due to pretrip activities. The use of devices such as dark or orange tinted goggles as well as portable phototherapy lamps can be considered to improve light and darkness exposure at proper times..

Short-term use of wake-promoting beverages and sleep promoting drugs (hypnotics, melatonin, melatonin receptor agonists) can be considered, especially upon arrival. The usefulness of exogenous melatonin to reduce jet lag symptoms is supported by a 2009 Cochrane review and several clinical reviews.[30] Low evening melatonin doses (0.5 mg) can be used for 3 days preceding an eastward trip to reset the clock and be followed by sleep-promoting doses at bedtime (3–5 mg) for 5 days upon arrival. This approach was reported to reduce the severity of jet lag symptoms by about 50%. Administration of ramelteon 1 mg (a MT_1 and MT_2 melatonin receptor agonist; not approved by Health Canada) at bedtime was shown to significantly reduce sleep onset latency 2-4 days after an eastward flight across 5 time zones.[31] Although trends were observed, this effect was not dose-dependent and no phase shift of the nocturnal melatonin rhythm was observed.

What is Delayed Sleep-Wake Phase Disorder (DSWPD)?

DSWPD is the most frequent intrinsic circadian rhythm disorder, affecting an estimated 0.1%–3.1% of the adult population and 7%–16% of adolescents and young adults.[32-35] When attempting to sleep at conventional times, people with DSWPD experience severe sleep onset insomnia, resulting in sleep restriction to 2–5 hours per night during work days and rebound sleep that can reach 9–18 hours over the ensuing rest days. Natural sleep onset is abnormally late (ie, around 3–6 am) and awakening around 10 am to 3 pm, with delayed core body temperature and melatonin rhythms.

Long circadian periods have been reported in DSWPD. People with DSWPD may have reduced sensitivity to the phase-advancing effect of morning light and/or increased sensitivity to the phase-delaying and melatonin suppressing effects of evening light.[32,34] DSWPD has been associated with polymorphisms of the circadian clock genes *PER3* and *CLOCK* and of the gene for arylalkylamine N-acetyltransferase, a rate-limiting enzyme in melatonin synthesis,[32] although the reported association is weak and DSWPD patients form a heterogeneous population. In addition to these circadian abnormalities, DSWPD patients appear to have impaired homeostatic drive for sleep and/or circadian modulation of sleep propensity resulting in increased difficult falling asleep at night. Exposure to light and late activity in the evening can delay circadian rhythms[36] and contribute to a delayed sleep-wake pattern.

A treatment strategy combining sleep hygiene, 1–2 hours of exposure to bright light in the morning, shielding from evening light, and evening ingestion of melatonin is recommended in patients with delayed circadian rhythms. Some people with DSWPD might have abnormally delayed rhythms, therefore bright light should be started several hours after the regular time of awakening and progressively advanced until the desired sleep time is achieved. Melatonin 5 mg taken between 7 pm and 9 pm for 4 weeks was successfully used to reduce sleep onset latency.[37] To maximize its phase-advancing effect, melatonin could be administered at 0.3–5 mg and given 5–7 hours prior to the desired bedtime.[37]

A strategy called chronotherapy has been proposed that consists of scheduling the patient to go to bed 3 hours later every day and to stabilize sleep to a 24-hour day when the desired bedtime is reached. This approach should not be the first choice as it increases the risk of converting the DSWPD into a more severe non-24-hour sleep-wake disorder.

What is Advanced Sleep-Wake Phase Disorder (ASWPD)?

ASWPD is considered a sleep-wake disorder of old age as sleep tends to stabilize at earlier times of day with age. It is less prevalent than DSWPD, with an estimated rate of 1% in middle-aged individuals. People with ASWPD complain of evening sleepiness, a need to go to bed early (ie, 6–9 pm), early morning awakenings (2–5 am), and reduced total sleep time.[32-35] Engaging in social activities in the evening can be problematic and sleep restriction tends to be worse on weekends.

Non-age related familial cases of ASWPD have been associated with a mutation in the *PER2* and casein kinase (CK) Iδ genes.[2,32] One study found a rest-activity cycle of 23.3 hours, suggesting that an abnormally short circadian period could be involved.[38] Decreased sensitivity to phase-delaying effects of light at night has been observed in older compared to younger individuals,[39] suggesting that similar mechanisms could contribute to ASWPD.

The treatment of choice for ASWPD is exposure to bright light for 1–3 hours in the evening and shielding from early morning light. Approaches such as chronotherapy and melatonin administration have been proprosed but are of arguable benefits.[34,35]

What is Non-24-Hour Sleep-Wake Disorder?

Non-24-hour sleep-wake disorder results from a failure of the endogenous circadian system to entrain to the environmental 24-hour day. It results in circadian rhythms that are free-running and severe cyclic sleep-wake disturbances as the circadian system comes in and out of phase with the sleep schedule. This condition is more common in blind people, 50% of whom fail to entrain to the 24-hour day.[40] It is usually associated with other psychiatric or neurological conditions in sighted individuals. In these individuals, this condition may be an exaggerated form of DSWPD and would share similar pathophysiological mechanisms.[34,35]

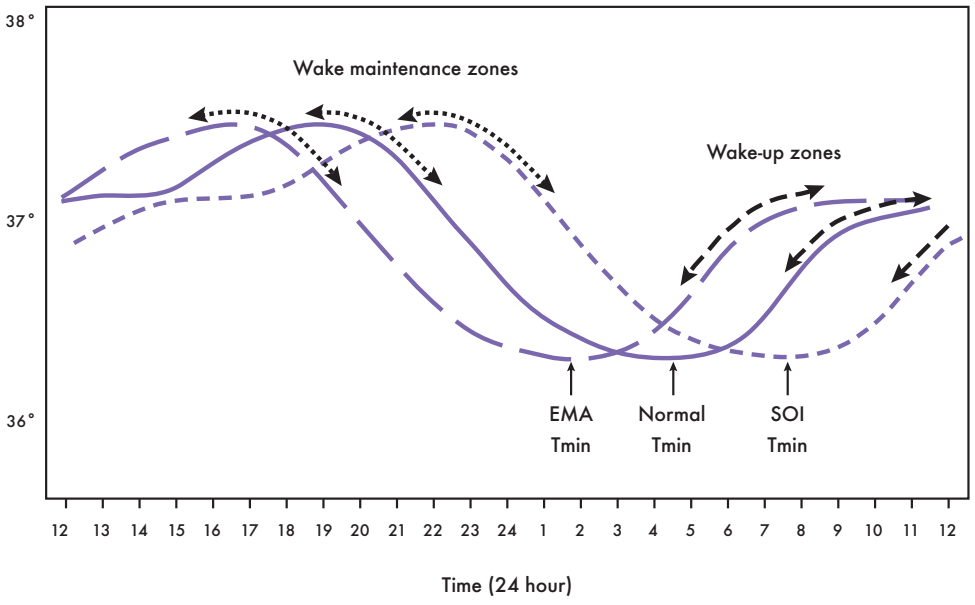
A combined approach with phototherapy in the morning, shielding from light in the evening, and melatonin (0.5–3 mg) in the evening is suggested to treat this condition. It should ideally be initiated when the endogenous circadian system is back in phase with the desired sleep schedule.[41] Implementing and maintaining a regular sleep-wake schedule with fixed bedtime and wake time is also recommended and could even be sufficient for blind individuals with a circadian period very close to 24 hours.

The Circadian View of Chronic Insomnia

Studies of people with either sleep onset insomnia or early morning awakenings revealed respective phase delays and advances of the endogenous circadian system relative to their desired sleep episode (Figure 1).[42] It has been suggested that nearly 55% of sleep onset insomniacs have delayed circadian rhythms,[42] due to an overlap with DSWPD and/or poor sleep hygiene. Bright light exposure in the morning has been successfully used to advance nocturnal melatonin and/or sleep onset times, reduce sleep latency, and improve sleep efficiency and duration.[42]

In middle-aged insomniacs, morning bright light exposure combined with sleep hygiene was shown to reduce sleep latency and increase total sleep time, although contradictory results were reported in older insomniacs.[43] Exposure to bright light in the evening in older women with mixed insomnia symptoms was also shown to progressively improve sleep onset, sleep efficiency and duration, although here again contradictory results were reported.[44] A review by Montgomery and Denis[45] examining the efficacy of bright light therapy in older adults (>60 years) with sleep complaints concluded that there is a lack of good quality evidence supporting the use of bright light therapy in this population.

Figure 1. Phase delays and advances of the endogenous circadian system.



A delay of the core body temperature circadian rhythm can produce sleep onset insomnia (SOI, dotted line), whereas an advance of the rhythm can lead to early morning awakening (EMA, dashed line). These rhythms and the displacement of the wake maintenance and wake-up zones are illustrated compared to those of good sleepers (solid line).

In seniors living in long-term care facilities, exposure to bright light in the morning has been shown to improve cognitive functioning without affecting daytime sleepiness.[46] However, contradictory results have been reported in dementia patients with exposure to bight light in the late morning. Care must be taken as bright light in the evening can also disturb nocturnal sleep and create daytime sleepiness.[47] One hour of bright light exposure at bedtime in Alzheimer disease patients was shown to improve sleep efficiency after 2 months of treatment but these effects were not sustained after 6 months.[48]

Studies showed that 70% of patients with attention deficit/hyperactivity disorder (ADHD) complain of sleep onset insomnia. This subgroup had delayed nocturnal melatonin rhythm, later sleep onset and wake time, and shorter sleep duration,[49] and may benefit from treatments recommended for DSWPD patients.

In comparison, patients with early morning awakenings can benefit from bright light exposure in the evening. This approach has been shown to delay nocturnal melatonin rhythm and final awakening and increase sleep duration.[42] The exact intensity, duration, time of administration and number of days of bright light treatment needed to achieve a stable sleep-wake pattern in DSWPD, ASWPD, and chronic insomnia requires further clinical testing.

Is Melatonin Effective as a Sleep Aid?

With sleep-maintenance insomnia, circadian phase misalignment or altered melatonin secretion are not always present such that the use of phototherapy and melatonin remains controversial. A meta-analysis of 19 studies looking at melatonin and melatonin receptor agonists in sleep disorders patients (including 14 with primary insomnia) revealed that 0.1–5 mg melatonin for 7–182 days reduced subjective and objective sleep onset latencies, and increased subjective but not objective total sleep time.[50] Overall, melatonin facilitates sleep onset but has subtle or no effects on sleep architecture. Even when used in the elderly, about 50% of whom complain of insomnia, 0.1–6 mg of melatonin taken orally showed mixed and arguable effects on nocturnal sleep. The sleep-promoting effect of melatonin is apparent when administered during the day but not at night when endogenous levels are high.[51] The use of melatonin is approved by Health Canada to alleviate sleep disturbances in adults suffering from sleep restriction or altered sleep schedules, but not to treat chronic insomnia. When recommended, 0.1–10 mg melatonin can be taken at bedtime for up to 4 weeks before consulting a healthcare practitioner.

At present, no prolonged-release melatonin formulation or selective melatoninergic receptor agonist is currently authorized by Health Canada. Ramelteon was the first melatonin agonist approved by the United States Food and Drug Administration. A meta-analysis of 8 studies on chronic insomniacs treated with ramelteon 4–32 mg for 2 days to 6 months revealed a slight reduction in subjective and objective sleep latencies and longer sleep duration compared to placebo.[52] Prolonged-release melatonin 2 mg is currently approved by the European Medicines Agency (EMA) for insomnia patients over the age of 55 years. In this population, 2 mg administered in the evening reduced PSG documented sleep onset latency[53] and increased subjective sleep quality and daytime alertness.[54] Tasimelteon, an MT_1 and MT_2 receptor agonist, was tested for transient insomnia induced by a 5-hour advance of the sleep-wake schedule.[55] Doses of 20 mg, 50 mg, or 100 mg given 30 minutes before bedtime for 3 days significantly reduced PSG sleep onset latency, and increased total sleep time and sleep efficiency compared to placebo. It also advanced the plasma melatonin rhythm in a dose-dependent manner, supporting its use for circadian rhythms sleep disorders.

A number of studies have shown that children are sensitive to the therapeutic effects of melatonin on sleep.[56,57] It can be used to alleviate sleep problems associated with autism spectrum disorders,[58] childhood DSWPD,[59] ADHD,[60] and chronic idiopathic childhood sleep onset insomnia.[61] To date, no change in mental health, sleep habits and pubertal development has been reported with long-term melatonin treatment (up to 4.6 years) in children and adolescents.[61]

Conclusion

People with chronic sleep disturbances can present with a slight misalignment between their endogenous circadian system and their scheduled sleep periods. Because of the daily distribution of high and low sleep propensity zones, such a circadian misalignment is sufficient to result in clinically relevant sleep onset and sleep maintenance difficulties. Interventions integrating sleep timing with circadian rhythms and sleep hygiene should be pursued as nonpharmacological approaches to enhance their sleep-wake quality.

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Abstract of Interest

Circadian adaptation to night shift work influences sleep, performance, mood and the autonomic modulation of the heart

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Our aim was to investigate how circadian adaptation to night shift work affects psychomotor performance, sleep, subjective alertness and mood, melatonin levels, and heart rate variability (HRV). Fifteen healthy police officers on patrol working rotating shifts participated to a bright light intervention study with 2 participants studied under two conditions. The participants entered the laboratory for 48 h before and after a series of 7 consecutive night shifts in the field. The nighttime and daytime sleep periods were scheduled during the first and second laboratory visit, respectively. The subjects were considered "adapted" to night shifts if their peak salivary melatonin occurred during their daytime sleep period during the second visit. The sleep duration and quality were comparable between laboratory visits in the adapted group, whereas they were reduced during visit 2 in the non-adapted group. Reaction speed was higher at the end of the waking period during the second laboratory visit in the adapted compared to the non-adapted group. Sleep onset latency (SOL) and subjective mood levels were significantly reduced and the LF:HF ratio during daytime sleep was significantly increased in the non-adapted group compared to the adapted group. Circadian adaptation to night shift work led to better performance, alertness and mood levels, longer daytime sleep, and lower sympathetic dominance during daytime sleep. These results suggest that the degree of circadian adaptation to night shift work is associated to different health indices. Longitudinal studies are required to investigate long-term clinical implications of circadian misalignment to atypical work schedules.

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