

Chronobiological Disorders: Current and Prevalent Conditions

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Abstract In recent decades, the hectic lifestyle of industrialized societies has wrought its effects on the quality of sleep, and these effects are evidenced by a profusion of sleep-related disorders. Regular exposure to artificial light, coupled with social and economic pressures have shortened the time spent asleep. Otherwise, Circadian Rhythm Sleep Disorders are characterized by desynchronization between the intrinsic circadian clock and the extrinsic cycles of light/dark and social activities. This desynchronization produces excessive sleepiness and insomnia. The International Classification of Sleep Disorders describes nine sleep disorders under the category of Circadian Rhythm Sleep Disorders. Currently, this diagnosis is made based on the patient's history, a sleep log alone, or the sleep logs and actigraphy conducted for at least 7 days. This review contains an overview of current treatment options, including chronotherapy, timed bright light exposure, and administration of exogenous melatonin.

Keywords Circadian rhythm sleep disorders · Delayed and advanced sleep phase disorders · Irregular sleep-wake rhythm · Free-running rhythm · Jet lag · Shift work

Introduction

The hectic lifestyles into which humans have been driven in recent decades have wrought their effects on the quality

of sleep, and these effects are visible as the knowledge of sleep-related disorders. In industrialized societies, regular exposure to artificial light, the advent of interactive activities like the internet and television, and social and economic pressures have shortened the amount of time spent asleep [1].

The most commonly observed sleep-wake behavior is to reduce sleep time during the working week, thereby accumulating a sleep debt, and then compensating for the sleep deficit by sleeping for a longer period of time on the weekend. During these nights, sleep shows high efficiency, short latency, and lengthened non-REM (NREM) slow wave stages. However, waking at a later time in the morning causes a phase delay the following day, which is often followed by an early wake-up time at the start of the working week [2]. Thus, the duration of sleep is substantially shortened and sleep deprivation returns [3].

Regularity in the timing of sleep and its duration is a rhythmic behavior regulated by complex physiological and psychological factors. The time selected to go to bed and awaken is clearly influenced by subjective needs, but the tendency to sleep at night and be active during the day is under a physiological control in the human species. The pattern of sleeping at night and being awake during the day is referred to as a diurnal pattern [4].

Because the secretion of melatonin at night occurs at the same time that humans need to sleep, the pineal gland has long been suspected of being involved in sleep. Indeed, the secretion of melatonin represents a biological rhythm and it is used as a marker of the biological clock. As research on the circadian system has progressed, several techniques have been developed to document the role of the circadian pacemaker in the regulation of physiological processes [5, 6]. Although melatonin secretion is influenced by the light–dark cycle, the diurnal rhythm of the pineal gland is

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directly controlled by an endogenous clock; this clock is likely the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The SCN is the central biological clock of the brain, and it generates and synchronizes overt biochemical, physiological, and behavioral rhythms throughout the body [7]. Determination of the rhythm of melatonin secretion may therefore reflect the internal perception of external conditions and provide a way to assess the temporal organization of the organism [4].

While circadian rhythms are part of normal physiology, some individuals have a desynchronization of the sleep-wake pattern. Different causes have been proposed for these abnormal patterns. For example, tumors in the SCN region or disturbances in sleep regulation, such as the total lack of sleep that characterizes fatal familial insomnia, may be at fault [8]. Misalignment has far-reaching consequences and can be very disruptive to familial and social life, as well as successful employment. Circadian rhythm sleep disorders are characterized by a desynchronization of the sleep-wake cycle and the external environment/social activity and this desynchronization can result in symptoms of excessive sleepiness and insomnia [8].

Since the clinical presentation of circadian rhythm sleep disorders is usually influenced by a combination of physiological, behavioral, and environmental factors, assessment strategies in circadian science involve physiological and behavioral evaluation. Core body temperature and the timing of melatonin secretion may be physiological markers to determine the circadian phase. Behavioral assessment involves sleep logs, actigraphy, and the Morningness-Eveningness Questionnaire [9]. Although no behavioral assessment is universally accepted, sleep logs are consistently recommended as a method for estimating the sleep schedule of patients. When used for 7 days or more, those sleep logs provide data regarding quantitative aspects of sleep [10]. Similarly, actigraphy, when used for at least 7 days, provides a longitudinal assessment of sleep patterns. While the Standards of Practice Committee of the American Academy of Sleep Medicine recommends actigraphy for evaluating patients suspected of circadian rhythm disorders, the strength of its recommendation varies from “Option” to “Guideline” depending on the suspected disorder [11]. This review attempts to assemble the characteristics of circadian rhythm sleep disorders, as well as provide an overview of current treatment options, including chronotherapy, timed bright light exposure, and administration of exogenous melatonin.

Circadian rhythm sleep disorders are among the eight categories listed in the International Classification of Sleep Disorders (ICSD-2) [12]. The main characteristic of this category is that the desired sleep time does not match the timing of the circadian rhythm of sleep and wake propensity. Misalignment between the timing of the individual’s

intrinsic circadian rhythm of sleep propensity and the 24-h social and physical environments may result in a chronic pattern of sleep disturbance. The presentation and severity of the circadian rhythm sleep disorders may be influenced by physiological factors, environmental factors, and maladaptive behaviors.

According to the ICSD-2 [12], circadian rhythm sleep disorder is defined by the following criteria:

- a. There is a persistent or recurrent pattern of sleep disturbance due primarily to one of the following: (1) alterations of the circadian timekeeping system or (2) misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.
- b. The circadian-related sleep disruption leads to insomnia, excessive daytime sleepiness, or both.
- c. The sleep disturbance is associated with impairment of social, occupational, or other areas of functioning.

The ICSD-2 [12] lists nine different sleep disorders in the category of circadian rhythm sleep disorder. All of these sleep disorders involve a sleep difficulty that meets each of the above criteria and are described as follows:

Circadian Rhythm Sleep Disorder: Delayed Sleep Phase Type (DSP)

This is characterized by habitual sleep-wake times that are delayed by 3–6 h relative to the desired or socially acceptable times [13]. The affected patient complains of difficulty falling asleep at a socially acceptable time; once sleep ensues, however, it is reported to be normal. The patient’s circadian phase of sleep is delayed but remains relatively stable when allowed to trail follow his or her preferred schedule. Attempts to fall asleep earlier may result in prolonged sleep latency or the development of secondary conditioned insomnia [14]. Patients with DSP disorder may complain of difficulty waking and confusion in the morning (“sleep drunkenness”) [15].

The prevalence of DSP in the general population is estimated to be between 0.13 [16] and 0.17% [17]. It is more common among adolescents and young adults, with a reported prevalence of 7–16% in this group [15]. It is estimated that DSP is observed in approximately 10% of patients with chronic insomnia in sleep clinics [10].

When using questionnaires such as the Morningness-Eveningness Questionnaire [9] to determine diurnal preferences, almost all individuals with DSP disorder are rated as evening types [13, 15]. Environmental factors, including decreased exposure to light in the morning or exposure to bright light late in the evening, may exacerbate the delayed circadian phase. Maladjustment to changes in work and

social schedules, travel across time zones, and shift work can precipitate this disorder. Individuals may use excessive caffeine or other stimulants, which may further delay sleep onset, and thereby, exacerbate the delayed sleep time.

The mechanisms responsible for DSP disorder are unknown, but DSP is due predominantly to a misalignment between circadian timing and the external environment. Abnormal interaction between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness has been reported to play an essential role in the pathophysiology of DSP. Some studies have demonstrated altered phase relationships relative to the light–dark cycle in patients with DSP disorder [18]. These patients presented with delays in sleep onset and offset and in the phase of circadian markers (e.g., core body temperature and melatonin) compared to controls. Either voluntary behavior, such as staying awake late at night and waking up late in the morning, or psychological profile, such as presence of depression, may result in an abnormal relationship between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness [19]. Delayed bed times and wake times may increase exposure to bright light in the late evening (a delay signal for the circadian clock) and decrease exposure to light in the early morning (an advance signal for the circadian clock). These changes promote and perpetuate the delay in the circadian sleep phase [20].

A positive family history is present in approximately 40% of individuals with DSP. Polymorphisms in the genes *hPer3*, arylalkylamine N-acetyltransferase, human leukocyte antigen (HLA), and *Clock* have been suggested to be associated with DSP [21].

Diagnosis is made primarily based on patient history, but a sleep log alone, or in conjunction with recordings of sleep logs and actigraphy over a period of at least 7 days, can demonstrate delayed sleep onset and offset. Daily demands and schedules may result in an earlier-than-desired waking time on weekdays, but a delay in bedtime and waking time is almost always observed on weekends and vacations [18].

Polysomnography is not routinely indicated for the diagnosis of DSP but may be useful in excluding other sleep disorders. When performed at preferred (delayed) sleep times, it is normal for age. If a conventional bedtime and wake-up time is enforced, however, prolonged sleep latency and decreased total sleep time are observed [22].

According to the ICSD-2 [12], the diagnosis of DSP disorder is based on the following criteria:

- a. There is a delay in the phase of the major sleep period in relation to the desired sleep time, and wake-up time as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock

time, together with the inability to awaken at a desired and socially acceptable time.

- b. When allowed choosing their preferred schedules, patients will exhibit normal sleep quality and duration for their age and maintain a delayed but stable phase of entrainment to the 24-h sleep-wake pattern.
- c. Sleep logs or actigraphy monitoring for at least 7 days demonstrate a stable delay in the timing of the habitual sleep period. In addition, a delay in the timing of other circadian-rhythms, such as the nadir of the core body temperature rhythm or dim light melatonin onset (DLMO), is useful for confirmation of the delayed phase.
- d. The sleep disturbance is not better explained by any other current sleep, medical, neurological, or mental disorder, use of medication, or substance abuse.

Treatment should be customized to the severity of symptoms, comorbid psychopathology, school schedules, work obligations, ability and compliance of the patient and family to conform to treatment, and social pressures [23]. Current treatment for DSP disorder includes several options. One is chronotherapy, that is a behavioral approach in which the circadian clock is reset by progressively delaying sleep and wake times by 3 h every 2 days, until the desired sleep and wake times are achieved and maintained by adhering to a set sleep–wake schedule and good sleep hygiene practices [13, 24, 25]. Unfortunately, there are no controlled trials supporting the efficacy or safety of this therapy [26]. One of the most commonly used treatments for DSP is timed bright light, but the optimal timing, duration, and dosing of morning light remain to be determined [26]. This approach causes a phase advance of the sleep onset time [27, 28]. The parameters most often recommended for this therapy are broad-spectrum bright light of 2,000–10,000 lux (most frequently 2,500 lux) for 1–3 h prior to, or at waking time. The effect of lower light doses, blue light, and other timings are not yet known [26]. In view of the clinical limitations encountered with chronotherapy and poor compliance with phototherapy, the therapy for DSP with exogenous melatonin (0.3–3 mg), administered 1.5–6 h before the habitual sleep time, has been investigated as a treatment venue [29]. Afternoon or evening administration of melatonin shifts circadian rhythms and the nadir of core body temperature to an earlier time [26, 30, 31]. The optimal time and dosing of melatonin administration have not yet been established. Some studies have used 5 mg [30–32], but another employed 0.3–3 mg [33]. Overall effectiveness can be improved by using a combination of chronotherapy, morning phototherapy and late afternoon or early evening melatonin [34]. Hypnotics before the habitual sleep time and stimulants at waking time have also been used to treat DSP disorder, but the evidence

on their efficacy and safety is insufficient to draw any conclusions [26].

Circadian Rhythm Sleep Disorder: Advanced Sleep Phase Type (ASP)

This is a stable advance of the major sleep period, characterized by habitual sleep onset and waking times that are several hours earlier than conventional and desired times. Patients affected with ASP complain of sleepiness in the late afternoon or early evening, early sleep onset, and spontaneous early morning awakening [35].

The prevalence of ASP in the general population is unknown. Non-age-related ASP is believed to be rare. However, the prevalence tends to increase with age and has been estimated at roughly 1% in middle-aged and older adults. Both genders are equally affected [36].

The exact pathophysiological mechanisms underlying ASP are unclear, but they may include an unusually short endogenous circadian period (less than 24 h) [37]. Genetic factors are likely to play an important role in the development of the condition. Environmental factors may precipitate, maintain, or exacerbate the advanced circadian phase. Several familial cases of ASP disorder have been identified [18, 38] and in all the families, the trait segregated with an autosomal dominant mode of inheritance [39]. A mutation in the circadian clock gene *hPer2* was identified in a large family with ASP [40]. The fact that other pedigrees do not carry this mutation suggests genetic heterogeneity [41].

Polysomnography is not routinely indicated for ASP, but it gives age-appropriate results when performed at the preferred (advanced) sleep times. However, polysomnography is an important assessment for comorbid sleep disorders, such as obstructive sleep apnea and periodic limb movements, which increase with age and may be associated with ASP [18].

An advance relative to the general population in the timing of the nadir of the core body temperature rhythm and DLMO are used in research to determine the phase of circadian rhythms [42], but the advance in waking time may, in fact be greater than the advance in these other circadian markers [43].

According to the ICSD-2 [12], the diagnosis of ASP disorder is based on the following criteria:

- a. There is an advance in the phase of the major sleep period relative to the desired sleep and wake-up times. This is evidenced by a chronic or recurrent complaint of the inability to stay awake until the desired conventional clock time, in addition to, an inability to remain asleep until the desired acceptable time for waking.

- b. When patients are allowed to choose their preferred schedules, sleep quality and duration are normal for age with an advanced but stable phase of entrainment to the 24-h sleep-wake pattern.
- c. Sleep log or actigraphy monitoring for at least 7 days demonstrates a stable advance in the timing of the habitual sleep period. In addition, an advance in the timing of other circadian-rhythm markers, such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the advanced circadian phase [3].
- d. The sleep disturbance is not better explained by any other current sleep, medical, neurological, or mental disorder, medication use, or substance abuse.

Current treatment for ASP includes the following options. One is chronotherapy, which progressively advances sleep time by 2 h every day until the desired sleep time is achieved [44]. The most commonly recommended treatment for ASP is timed bright light exposure, which is done in the evening, usually between 7 and 9 pm [28]. However, the efficacy of this approach as a treatment for ASP disorder is controversial. Although Palmer et al. [45] and Suhner et al. [46] found no difference between light therapy and placebo, other studies showed positive results with this approach [47–50]. A third option is melatonin, which can be administered in the early morning to delay the timing of circadian rhythms in individuals with ASP disorder. However, taking melatonin too close to waking time may result in residual sedation the next day. Overall, the evidence for the efficacy of this treatment is weak or contradictory [26].

Circadian Rhythm Sleep Disorder: Irregular Sleep-wake Type

This is characterized by the lack of an identifiable circadian rhythm of sleep and wake times. Sleep and wake periods are variable throughout the 24-h period, and affected patients usually experience insomnia and excessive sleepiness depending on the time of day. The prevalence of this disorder in the general population is unknown, but it is thought to be rare. Onset of the condition may occur at any age. Although the total sleep time may be normal for the patient's age, napping is usually prevalent throughout the 24-h period in individuals with irregular sleep-wake disorder [51].

Limited knowledge is available regarding the course and complications of irregular sleep-wake disorder. Predisposing or precipitating factors in the development of irregular sleep-wake disorder include poor sleep hygiene and lack of exposure to external synchronizing agents such as light,

activity, and social schedules. These factors are particularly important in the institutionalized elderly [52]. However, anatomical and functional abnormalities of the circadian clock can result in an arrhythmic pattern of rest and activity.

Multiple, irregular sleep and wake periods throughout the 24-h period are observed by monitoring the sleep logs and actigraphy, and screening shows the expected lack of a circadian rhythm of the sleep-wake cycle [11, 53]. Monitoring polysomnography and other circadian rhythms such as core body temperature for at least 24 h may also reveal a loss of clear circadian rhythmicity [51].

According to the ICSD-2 [12], the diagnosis of irregular sleep-wake disorder is based on the following criteria:

- a. There is a chronic complaint of insomnia, excessive sleepiness, or both.
- b. Sleep log or actigraphy monitoring for at least 7 days demonstrates multiple irregular sleep bouts (at least three) in a 24-h period.
- c. Total sleep time per 24-h period is essentially normal for age.
- d. The sleep disturbance is not better explained by any other current sleep, medical, neurological, or mental disorder, medication use, or substance abuse.

Treatment strategies for this disorder involve increasing the intensity and duration of light exposure during the day [54]. The majority of studies found positive effects on circadian rest-activity rhythms or sleep with bright light exposure (2 h, 1,500–8,000 lux) [55–58]. Different studies examined different exposure times: morning, evening, both morning and evening, or throughout the day. In contrast, there is no evidence that melatonin administration improves sleep for patients with irregular sleep-wake disorder [59, 60]. The recommended treatment for this disease involves a combination of methods, including sunlight exposure, physical activities, structured bed-time routine, and decreased night-time noise and light [61, 62].

Circadian Rhythm Sleep Disorder: Free-running Type (Nonentrained Type)

This is characterized by major daily fluctuations in sleep and wake times. The free-running type usually reports a progressive delay in the timing of sleep and wake times. This delay is a consequence of the fact that the endogenous circadian period in humans is typically slightly longer than 24 h. Sleep symptoms occur because the intrinsic circadian pacemaker is neither entrained to a 24-h period or is free running over a 24-h period.

The sleep patterns of patients with free-running type can be quite variable. Some individuals adopt a sleep pattern

that is congruent with their free-running pacemaker. These individuals shift their sleep times each day in concert with their circadian rhythms. When the endogenous circadian rhythm is in phase with sleep times, the sleep pattern is usually normal.

It is thought that over half of totally blind individuals have nonentrained circadian rhythms [63]. Almost 70% of blind people complain of chronic sleep disturbances, and 40% have chronic cyclic sleep disturbances. Rare cases of this disorder have been described in sighted people, but the actual incidence of this disorder is unknown. There are no known gender differences [64].

The most likely cause of nonentrained circadian rhythms in blind people is decreased or absent photoreception. Despite the absence of visual light perception, however, the circadian clock of some blind individuals can respond to bright light [65]. In sighted people, social and behavioral factors may also play an important role in the development and maintenance of the disorder. Patients with this disorder show an increased incidence of psychiatric and personality disorders [18], and the disorder is occasionally associated with mental retardation or dementia [66]. It has also been suggested that DSP disorder and nonentrained circadian rhythms may overlap. This hypothesis is supported by reports of a few DSP patients who developed free-running rhythms after chronotherapy [67].

The lack of a stable relationship between the sleep-wake cycle and the 24-h day may be demonstrated by monitoring a sleep log and performing actigraphy over prolonged periods [11]. Actigraphy and polysomnography are usually normal for age, but sleep onset and wake times are typically delayed each day, when patients are allowed to follow their endogenous sleep schedules [18].

According to the ICSD-2 [12], the diagnosis of circadian rhythm sleep disorder of the free-running type is based on the following criteria:

- a. There is a chronic complaint of insomnia or excessive sleepiness related to abnormal synchronization between the 24-h light-dark cycle and endogenous circadian rhythm of the sleep and wake propensity.
- b. Sleep log or actigraphy monitoring for at least 7 days demonstrates a pattern of sleep and wake times that typically delays each day with a period longer than 24-h. Monitoring sleep logs or actigraphy for over 7 days is preferred in order to clearly establish the daily drift.
- c. The sleep disturbance is not better explained by any other current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance abuse.

Treatment options of this disorder in blind people include attempting to synchronize the circadian pacemaker by using behavioral approaches, maintaining a regular

schedule, or using pharmacological approaches like melatonin. Melatonin 10 mg given 1 h before bedtime has been shown to synchronize sleep–wake behaviors to a 24-h period in blind people with non-entrained circadian patterns [68]. Entrainment can be maintained with lower doses of 0.5 mg of melatonin given nightly [69]. Prescribed sleep–wake scheduling as a method to improve circadian rhythms may be a useful therapy for free-running disorder in sighted individuals, but there have been no clinical trials to test the efficacy of this intervention [26]. Time light exposure may be used to treat free-running disorder in sighted individuals, but the findings of the studies were not consistent [70–73]. The treatment of the free-running type of this disorder with melatonin has been shown to entrain rhythms successfully. The doses, timing, and duration of treatment vary between studies [68, 69, 74–78].

Circadian Rhythm Sleep Disorder: Jet Lag Type

This disorder results when the external environment of the sleep/wake cycle is temporarily changed to a new phase relationship with the endogenous circadian rhythm. This change is caused by rapid travel across time zones. Individuals complain of fatigue and decreased subjective alertness, night-time insomnia, mood changes, difficulty concentrating, and gastrointestinal problems [79]. Some of these symptoms may also be related to high-altitude jet travel. Symptoms are transient and should resolve as the traveler's circadian clock re-establishes a normal phase relationship with the local time. The severity of symptoms is dependent on the number of time zones traveled and the direction of travel. Eastward travel produces more complaints of difficulty falling asleep, whereas complaints of inability to maintain desired sleep patterns are most common when traveling westward [80].

Although there is substantial inter-individual variability in the severity of jet lag symptoms, all age groups are affected. Symptoms in the elderly may be more pronounced, however, and the rate of recovery may be slower than in younger adults [81]. Discomfort during the menstrual cycle has been associated with frequent travel in female airline personnel [82]. The use of hypnotics in association with alcohol to treat symptoms of jet lag has been associated with amnesia [79].

The severity of insomnia and impaired alertness associated with transmeridian travel may be increased by prolonged uncomfortable sitting positions, air quality and pressure, stress, sleep deprivation, and excessive intake of caffeine and alcohol [79].

Laboratory testing is usually not indicated for this disorder. Actigraphy or polysomnography can be used to observe the loss of a normal sleep–wake pattern or a

mismatch between the timing of sleep and wakefulness and the desired sleep–wake pattern based on local time [11].

According to the ICSD-2 [26], the diagnosis of circadian rhythm sleep disorder of the jet lag type is based on the following criteria:

- a. There is a chronic complaint of insomnia or excessive sleepiness associated with transmeridian jet travel across at least two zones.
- b. An associated impairment of daytime function, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance) through one zone arises within 2 days after travel.
- c. The sleep disturbance is not better explained by any other current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance abuse.

When time at the destination is expected to be brief (2 days or less), maintaining home-base sleep hours may reduce sleepiness and jet lag symptoms [26, 83]. Effective and practical strategies to combat jet lag symptoms and improve performance and safety are needed. The combination of morning exposure to 3.5 h of bright light of more than 3,000 lux and a shift in the schedule 1 h earlier each day for 3 days prior to eastward travel may lessen the symptoms of jet lag [84]. The opposite approach—two evenings of light treatment at 3,000 lux for 3 h followed by bedtime based on local time at the destination—produced a greater phase delay after a westward flight [85]. Studies of patient populations with intention to treat analyses are lacking [26]. A combination of approaches intended to accelerate circadian alignment (e.g., timed light exposure) and behavioral strategies like adequate hydration, avoidance of caffeine and alcohol, and good sleep hygiene may minimize symptoms. The use of melatonin is controversial in this circadian rhythm sleep disorder [86]. But in another study, melatonin has been shown to alleviate jet lag symptoms with doses of 0.5–5 mg taken close to local bedtime for up to 4 days [80]. The short-term use of short-acting non-benzodiazepine hypnotic medications can be useful in alleviating symptoms of insomnia, and caffeine is often consumed to improve alertness. However, the combination of melatonin and zolpidem did not significantly improve symptoms of jet lag, and it was associated with increased adverse effects when compared to melatonin alone [87].

Circadian Rhythm Sleep Disorder: Shift Work Type

This disorder is characterized by complaints of excessive sleepiness or insomnia that occur in relation to work hours that are scheduled during the usual sleep period. The sleep

disturbance is most commonly reported in association with night and early morning shifts (before 6 a.m.). The total sleep time is typically truncated, and sleep quality is perceived as unsatisfactory [88]. Chronic sleep deprivation is associated with an impairment of performance at work, and reduced alertness may also affect the individual's safety [89–91]. In addition, major portions of free time may have to be used for recovery of sleep; this allocation of time has negative social consequences [92].

The prevalence of shift work disorder is associated with the prevalence of shift work among the population. In industrialized countries, it has been estimated that 20% of the workforce works during non-standard hours [93]. A recent study suggests that the prevalence of shift work sleep disorder is 2–10% in night and rotating shift workers [94]. These figures do not, however, include individuals with early morning work; these individuals may comprise yet another at-risk group. There is no known gender difference in vulnerability [95].

Because there are so many different work schedules ranging from an occasional overnight shift to regular night work, the course of this disorder is quite variable [96]. Since shift work is often combined with extended hours of duty, fatigue can be a complicating factor [97]. Exposure to light at the wrong time of the day and the tendency of most workers to resume full daytime activities and night-time sleep during weekends and vacations may work against circadian adaptation. Complications may include exacerbation of gastrointestinal [98] and cardiovascular disorders [99], as well as, increased risk for metabolic disturbances [100] and cancer [101]. Disruptions of social and family life are frequent. Drug and alcohol dependency may result from attempts to improve the sleep and wakefulness disturbances produced by shift work. The level of alertness required of the worker, in addition to the intensity of the symptoms, needs to be taken into account when evaluating this disorder [90].

Not all shift workers have sleep difficulties severe enough to interfere with work performance or social functioning. The ability to cope with shift work varies from individual to individual and is influenced by multiple factors, such as age, type of work schedule, commuting times, diurnal preference, and domestic/family responsibilities [96]. The condition is directly related to the sleep-generated interface by a circadian alerting process that corresponds with the time that the worker needs to sleep. Excessive sleepiness during the night appears to be partly related to cumulative sleep loss and partly related to a decreased circadian alerting signal that corresponds to work time. Thus, tolerance to night work varies considerably and may involve differences in the degree of circadian adaptation (“clock resetting”) to a night-work, day-sleep schedule [102]. Alternatively, tolerance may be related to individual differences in the relative balance of circadian

and homeostatic influences on sleep and wake regulation [92].

Diagnosis of shift work disorder is based on a temporal relationship between history and clinical presentation. Polysomnographic recordings may be useful if the sleep disorder is severe or the etiology of the sleep disturbance is in question. The sleep recording may be performed during the habitual “shifted” sleep period, and monitoring of an episode of usual daytime wakefulness/night sleep during a daytime shift is ideal for comparative purposes [94]. The sleep period may be fragmented, with prolonged sleep latency or shortened total sleep time, frequent arousals, and awakenings. The Multiple Sleep Latency Test usually demonstrates excessive sleepiness during the time of the work shift [103]. Sleep logs, actigraphy, and measures like the 24-h core body temperature rhythm are very useful in demonstrating a disrupted sleep-wake pattern consistent with shift work sleep disorder [11].

According to the ICSD-2 [12], the diagnostic of circadian rhythm sleep disorder of the shift work type is based on the following criteria:

- a. There is a chronic complaint of insomnia or excessive sleepiness that is associated with a recurring work schedule that overlaps the usual time for sleep.
- b. The symptoms are associated with the shift-work schedule over the course of at least 1 month.
- c. Sleep logs or actigraphy monitoring for at least 7 days, demonstrates disturbed circadian and sleep-time misalignment.
- d. The sleep disturbance is not better explained by any other current sleep, medical, neurological, and mental disorders, medication use, or substance abuse.

Treatment for shift work disorder may include the following options. One is behavioral strategies, such as good sleep hygiene, wearing sunglasses while commuting home, and optimizing the sleep environment. Some studies have shown that napping, including early sleep periods prior to starting a shift, increased alertness and vigilance and improved reaction times. This napping also decreased accidents during night shift work [26, 104]. Another option is bright light exposure during the night shift using intensities of 2,350–12,000 lux administered in various schedules. Both this exposure therapy and light restriction in the morning have been shown to lead to subjective improvements in work time performance tasks, alertness, and mood compared to ordinary light exposure [26]. A third option is administration of melatonin in doses of 1.8–3 mg prior to daytime sleep after night work shifts. This approach has been shown to improve daytime sleep quality and duration, but it failed to enhance alertness at night [26, 105–108].

A fourth option is to use hypnotic medications to promote daytime sleep among night shift workers. However,

the balance of risks and benefits for this therapy is unclear [26]. A fifth approach is to administer stimulants like caffeine or modafinil (200 mg) at the beginning of the shift [109, 110]. Lastly, treatment of co-morbid sleep related disorders may also improve symptoms [103, 111].

Circadian Rhythm Sleep Disorder due to a Medical Condition

The etiology and prevalence of this disorder are associated with an underlying primary medical or neurological condition. Decreased exposure to light and structured physical and social activities may influence the severity of the condition. The disruption of the sleep-wake cycle leads to poor sleep quality and impaired neurocognitive and physical performance.

Several medical and neurological conditions have been associated with circadian rhythm disturbances. One condition is dementia: the disruption of the sleep-wake cycle has been implicated in the etiology of “sundowning” and nocturnal wandering in this patient population [112]. Another condition is blindness: blind people with a free-running rhythm should be diagnosed with circadian rhythm sleep disorder of the free-running type. A third condition is hepatic encephalopathy; patients with liver cirrhosis complain of insomnia and excessive sleepiness. In fact, these patients may exhibit a pattern of circadian rhythm sleep disorder of the delayed sleep phase type [113].

According to the ICSD-2 [12], the diagnosis of circadian rhythm sleep disorder due to a medical condition is based on the following criteria:

- a. There is a chronic complaint of insomnia or excessive sleepiness related to alterations of the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the tuning or duration of sleep.
- b. An underlying medical or neurological disorder predominantly accounts for the circadian rhythm sleep disorder.
- c. Sleep logs or actigraphy monitoring for at least 7 days demonstrates disturbed or low amplitude circadian rhythmicity.
- d. The sleep disturbance is not better explained by any other current sleep or mental disorder, medication use, or substance abuse.

Determination of the diagnosis and treatment of circadian rhythm sleep disorder due to a medical condition is troublesome, because doctors must ascertain whether the primary cause is a medical or neurological disorder or a change in exposure to circadian synchronizing agents like light and activity.

Other Circadian Rhythm Sleep Disorders

According to the ICSD-2 [12], this disorder included those that (1) satisfy the criteria of a circadian rhythm sleep disorder as defined before, (2) are not due to drug or substance use, and (3) do not meet the criteria for other circadian rhythm sleep disorders as classified by the ICSD-2.

Other Circadian Rhythm Sleep Disorders due to Drug or Substance Use

According to the ICSD-2 [12], this category includes disorders that (1) satisfy the general criteria of a circadian rhythm sleep disorder as defined before, (2) are due to drug or substance use, and (3) do not meet the criteria for other circadian rhythm sleep disorders as classified by the ICSD-2.

Conclusions

The sleep and wakefulness cycle is a major circadian rhythm in humans. Optimal sleep results when bedtime coincides with the phase of the cycle that physiologically predisposes one to sleep. A disorder of the circadian sleep rhythm can only be considered when there is chronic failure to fall asleep at the optimal time. The existence of a disorder is evidenced by insomnia, excessive daytime sleepiness, and an impairment of cognitive and motor functions. The exact diagnosis and adequate treatment of circadian rhythm sleep disorders is very important, but rigorous studies are needed to test the reliability and validity of the ICSD-2 [12] diagnostic criteria and the reproducibility of treatment results in specific disorders. For example, more research with large samples of subjects with jet lag is needed to determine the clinical feasibility of a program of timed light exposure scheduled prior to travel or on arrival at a traveler’s destination. Studies on the effects of hypnotics and caffeine on daytime symptoms are also necessary. Studies on shift work disorder are required to support the use of planned napping, before or on the job, to counteract sleepiness during shift work. In addition, large randomized, controlled, clinical trials on the efficacy of light exposure (and blue light exposure) in resetting the circadian clock in different patient populations, is needed. These studies should examine patients diagnosed with circadian rhythm sleep disorder of the shift work, ASP, DSP, and free-running types.

Administration of melatonin, hypnotics, and alertness-promoting stimulant medications should also be explored. Clinical trials should be conducted with patients showing irregular sleep-wake rhythm disorder in order to test

strategies for structuring and reinforcing relevant circadian time cues in order to increase the amplitude of the circadian cycle.

The detrimental effects caused by the impossibility of reconciling sleep needs with social demands have far-reaching consequences. The investigation of how sleep loss affects modern life is a rather new science, but the topic has attracted the attention of the scientists, economists, and politicians. It is a particularly important problem, since many ailments that reach epidemic proportions, such as diabetes mellitus type II, obesity, and obesity's downstream disorders, have been linked to loss of sleep. As a result, scientific production in the field has been intense, since sleep loss will most likely continue to be a major affliction.

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