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REVIEW ARTICLE

Treatment of Circadian Rhythm Sleep–Wake Disorders

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Abstract: Circadian rhythm sleep-wake disorders (CRSWDs) are a distinct class of sleep disorders caused by alterations to the circadian time-keeping system, its entrainment mechanisms, or a mismatch between the endogenous circadian rhythm and the external environment. The main clinical manifestations are insomnia and excessive daytime sleepiness that often lead to clinically meaningful distress or cause mental, physical, social, occupational, educational, or other functional impairment. CRSWDs are easily mistaken for insomnia or early waking up, resulting in inappropriate treatment. CRSWDs can be roughly divided into two categories, namely, intrinsic CRSWDs, in which sleep disturbances are caused by alterations to the endogenous circadian rhythm system due to chronic changes in the regulation or capture mechanism of the biological clock, and extrinsic circadian rhythm sleep-wake disorders, in which sleep disorders, such as jet lag or shift-work disorder, result from environmental changes that cause a mismatch between sleep-wakefulness times and internal circadian rhythms. Sleep diaries, actigraphy, and determination of day and night phase markers (dim light melatonin onset and core body temperature minimum) have all become routine diagnostic methods for CRSWDs. Common treatments for CRSWD currently include sleep health education, time therapy, light therapy, melatonin, and hypnotic drug therapy. Here, we review the progress in the epidemiology, etiology, diagnostic evaluation, diagnostic criteria, and treatment of intrinsic CRSWD, with emphasis on the latter, in the hope of bolstering the clinical diagnosis and treatment of CRSWDs.

Keywords: Circadian rhythm, sleep-wake disorders, etiology, diagnostic evaluation, treatments, melatonin.

1. INTRODUCTION

Biological organisms have strict organization and regularity in time and space. Molecules, cells, organs, systems, and behaviors all undergo oscillating changes in a specific time sequence, called the biological rhythm. According to the length of the cycle, the biological rhythm can be divided into three main types, namely, infradian rhythm, ultradian rhythm, and circadian rhythm. The latter is inherent to the body and has endogenous manifestations; consequently, understanding related disorders has become the focus of intensive research [1]. The circadian rhythm, also referred to as the near-24-hour rhythm, is widespread in the biological world, with most organisms exhibiting circadian rhythms of behavior and physiology. The circadian rhythm requires daily adjustment of the internal clock because the endogenous frequency of human physiological cycle oscillations is slightly longer than 24 hours, which is not consistent with the 24-hour environmental cycle. This coordination is achieved through a central pacemaker located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [2].

The circadian clock system plays an important role in maintaining physiological functions, including the sleep-wake cycle, body temperature, metabolism, and organ functions [3]. The sleep-wake cycle is the most prominent of these circadian behavioral functions. The confinement of sleep to the night or day in diurnal and nocturnal species, respectively, is directly controlled by the SCN, the main circadian clock. The SCN projects to sleep-regulating brain regions, such as the ventrolateral preoptic nucleus, the lateral hypothalamus, and the locus coeruleus, *via* the sub-paraventricular zone and the dorsomedial hypothalamus [4]. The circadian clock subsequently regulates sleep timing, leading to early (lark) and late (owl) chronotypes. Clock gene polymorphisms are associated with sleep disorders (*e.g.*, delayed sleep phase disorder) [5-7]. Besides sleep timing, the SCN clock also affects sleep architecture; for example, REM sleep predominantly occurs during the nadir of the SCN-controlled circadian rhythm of core body temperature [8, 9].

The sleep and wake cycle is the classic example of circadian rhythm systems, the generation, maintenance, and consolidation of which depend on the interaction between endogenous circadian rhythms and processes that regulate the homeostasis of the internal environment. Internal circadian rhythms determine the amount of sleep, while homeostasis

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generally determines the quality of sleep. When the two systems are in a state of balance, the individual can remain awake for a long time during the day (approximately 16 hours) and maintain a long and stable sleep at night (approximately 8 hours) [10]. Alterations to either of these processes, or to the interaction between them, can result in insomnia and (or) excessive sleepiness [11]. The International Classification of Sleep Disorders Third Edition (ICSD-3), released by the American Academy of Sleep Medicine in 2014, refers to such sleep disorders as circadian rhythm sleep-wake disorders (CRSWDs), that is, sleep disorders that occur due to disturbances in the individual's own circadian rhythm or those that arise due to inconsistencies between the latter and the external circadian rhythm. According to the ICSD-3 classification criteria, CRSWDs can be roughly divided into two categories: one is caused by alterations in the endogenous circadian rhythm system resulting from chronic changes in the regulation or capture mechanism of the biological clock, while the other results from a mismatch between the sleep-wake time and the internal circadian rhythm attributable to environmental changes [12].

2. DATA SOURCES

A systematic review approach was utilised to provide a comprehensive overview of existing research evidence about the treatment of circadian rhythm sleep-wake disorders.

A comprehensive search strategy was conducted in the PubMed database from its inception to 31 March 2021.

The search strategy involved the primary keyword "Circadian rhythm","Sleep-wake disorders", "Delayed sleep-wake phase disorder", "Advanced sleep-wake phase disorder", "Non-24-hour sleep-wake rhythm disorder", "Irregular sleep-wake rhythm disorder", "Diagnostic evaluation", "Treatments" and the total yield is 724 papers. At the same time we also reviewed the reference lists of relevant primary papers and reviews to identify studies that may have been missed in the search. Finally, 119 articles were adopted. Because each section of the article has duplicate content, the specific number of papers cannot be determined for each section.

3. DELAYED SLEEP-WAKE PHASE DISORDER

3.1. Definition

Delayed sleep-wake phase disorder (DSWPD), also called delayed sleep phase syndrome, is a common form of CRSWD. It is mainly manifested as a delay in an individual's sleep onset and wake time of 2 hours or more beyond what is considered ideal and compared with a normal individual [13]. DSWPD can lead to sleep-onset insomnia at night or difficulty waking up in the morning. Individuals with this disorder exhibit significant daytime functional (*e.g.*, excessive daytime sleepiness, fatigue, low mood) and cognitive (*e.g.*, concentration, memory, and attention) impairments. However, when their sleep schedules are not restricted by social requirements, they show normal sleep structure and sleep duration [5].

3.2. Epidemiology

As the overall prevalence of DSWPD varies according to the type of population being evaluated, its exact prevalence is unclear. In an early study encompassing 10,000 Norwegian adults aged 18–67 years, the prevalence was found to be 0.17%, with an average age of onset of 15.4 years [14]. In an epidemiological study based on Japanese students, the prevalence of DSWPD was estimated to be 0.48%, without gender differences. Moreover, in universities, DSWPD prevalence was reported to be higher among senior students (1.66%) than junior students (0.09%) [15]. In a large-scale population study conducted in Hordaland County in Norway in 2012, the prevalence of DSWPD among 10,220 adolescents aged 16–18 years (54% girls) was 3.3% and was significantly higher among girls (3.7%) than boys (2.7%) [16]. In a recent population study of adults in New Zealand, the prevalence of sleep delay types ranged from 1.5% to 8.9%, declining with age [17].

3.3. Etiology

The exact etiology of DSWPD is unknown, and many factors are thought to contribute to its development, including genetic, environmental, and behavioral factors. Approximately 40% of DSWPD patients have a family history of CRSD or sleep phase delay. It has been reported to be inherited in an autosomal dominant manner and is strongly associated with mutations in period circadian regulator 3 (*PER3*) and other clock genes [5]. A recent study further showed that the inheritance of DSWPD is associated with a dominant coding variation in the core circadian clock gene cryptochrome 1 (*CRY1*), which produces a transcriptional inhibitor with an enhanced affinity for the rhythm-activating proteins CLOCK and BMAL1. This allele is found in 0.6% of the population and may play an important role in DSWPD by lengthening the circadian period [18]. Environmental factors, including a lack of daylight in the morning and an increase in light exposure at night, are thought to contribute to the development of delayed sleep stage types [19]. Behavioral factors such as night-shift work, excessive caffeine consumption, poor sleeping habits, reduced amounts of morning light, or heavy exposure to bright lights or electronic screens at night can also cause a shift in sleep patterns [20]. Auger *et al.* showed that people with DSWPD received more light at night and less in the morning compared with unaffected controls. The authors further suggested that DSWPD individuals may have a behavioral tendency to avoid light in the morning [21]. Additionally, recent studies have highlighted that a causal relationship may exist between DSWPD and individual personality characteristics [22].

3.4. Diagnostic Evaluation

The diagnosis of DSWPD is mainly based on clinical symptoms. The assessment tools that can be used to diagnose DSWPD in the clinic include sleep diaries, actigraphy, circadian rhythm marker measurement, the morningness-eveningness questionnaire (MEQ), and polysomnography (PSG), each with its strengths and weaknesses. The sleep diary can record some of the patient's sleep parameters, including when lights are turned out when the patient goes to bed, sleep latency, wake after sleep onset, and wake time in the morning and wake up in the morning to objectively evaluate the patient's sleep [12]. In addition, the sleep diary can contain subjective data about daytime functions (such as fatigue and drowsiness) and factors that can affect sleep (such as drug use, alcohol, and caffeine intake) to allow a

full understanding of the factors affecting the patient's sleep-wake time. However, this tool is not suitable for use with patients that cannot complete the sleep diary, such as elderly people with cognitive impairment [23]. An actigraph, commonly worn on the patient's wrist, records the patient's activities and light exposure, supplementing the objective data of the sleep diary. Both activities and light exposure are recorded for at least 7 consecutive days, preferably 14 days, including both working and non-working days [24]. For the determination of circadian rhythm markers, the most commonly used method is the measurement of the timing of dim light melatonin onset (DLMO); however, the cost and burden of collecting DLMO data significantly limits the use of this method in many clinical settings [25]. The MEQ can also be used to assess whether an individual's sleep habits conform to a morning-type or a night-type preference; however, its clinical value is yet to be evaluated [26]. DSWPD is often misdiagnosed as chronic insomnia due to problems with sleep initiation. Unlike insomniacs, however, when DSWPD patients are allowed to sleep as they wish, the sleep structure will be basically the same as that of the normal population of the same age group. In such cases, PSG can be selectively used as an evaluation method for DSWPD but is not done so routinely [12].

3.5. Diagnostic Criteria

The diagnosis of DSWPD requires that the following five main criteria are met [12]:

1) There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep onset time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of the inability to fall asleep and difficulty awakening at a desired or required clock time; 2) the symptoms are present for at least 3 months; 3) when patients are allowed to choose their schedule *ad libitum*, they will exhibit improved sleep quality and duration and maintain a delayed phase of the 24-h sleep-wake pattern; 4) sleep logs and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) consisting of work/school days and free days, demonstrate a delay in the timing of the habitual sleep period; and 5) the sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

3.6. Treatments

If the sleep pattern of the patient is consistent with their work or social time, treatment is unnecessary. The overall goal of DSWPD treatment is to readjust the biological rhythm to the ideal 24-hour day/night cycle. The current main treatment methods for DSWPD are shown in Table **1**.

3.6.1. Melatonin Treatment

Melatonin is a "darkness signal" secreted by the pineal gland and serves as an endogenous zeitgeber that regulates the circadian rhythm of certain physiological functions of the body, thereby promoting sleep. Melatonin secretion is higher during the night than in the morning or in the light. Using melatonin at the right time can change the sleep cycle [27, 28]. Rahman *et al.* reported that the administration of 5 mg of melatonin to patients with DSWPD and depression for 4 weeks significantly reduced their depressive symptoms and improved sleep [29]. Nagtegaal *et al.* undertook a placebo, double-blind cross-over trial on 30 patients, and found that 5 mg melatonin administration could advance the endogenous melatonin secretion time by 1.5 hours. PSG analysis indicated that the sleep onset time of patients was advanced, and the sleep latency was shortened; in contrast, the sleep structure was not affected. During the treatment, the clarity of patients after waking up in the morning was significantly improved, as was their quality of life [30]. Similarly, in 2010, a meta-analysis of the effects of melatonin on DSWPD by Geijlswijk and colleagues showed that melatonin treatment advanced the secretion of endogenous melatonin by 1.18 hours on average, reduced sleep onset latency by 23 minutes, and advanced sleep onset time by 0.67 hours. Moreover, the authors recommended that small doses (0.3~5.0 mg) of melatonin should be given 3–6 hours before DLMO to avoid high melatonin levels late at night or early in the morning [31]. A recent study showed that 0.5 mg of melatonin combined with behavioral wake-up scheduling can advance sleep onset time, improve sleep quality, and reduce sleep-related disorders and daytime dysfunction. This was the largest placebo-controlled trial to date evaluating the clinical efficacy of melatonin in improving sleep initiation and sleep quality in DSWPD [32]. Unfortunately, if melatonin is stopped, patients with DSWPD may experience a recurrence of symptoms [33, 34], the time of recurrence being related to the severity of the preconditioning circadian rhythm delay [35]. Recently, a statement from the American Academy of Sleep Medicine highlighted the lack of available melatonin-related evidence regarding CRSD treatment. A systematic review of existing research indicated that melatonin given to children and adolescents to treat DSWPD elicited only moderate effects when administered alone [36]. In general, melatonin is well tolerated and has few side effects, the most commonly reported being headache and nasopharyngitis. Nevertheless, owing to a lack of safety data, melatonin should be avoided during pregnancy and breastfeeding, and should also be administered with caution in patients with liver injury. To date, no serious adverse reactions to melatonin administration have been reported. Two observational, long-term studies on children and adolescents (average follow-up of 4 years) also did not document any safety issues [37, 38].

Several studies have evaluated the combined effects of light and melatonin. In one study, subjects took 0.5 mg of melatonin 5 hours before bedtime and received 30 minutes, 1 hour, or 2 hours of intense light (5,000 lux). Subjects exposed to strong light for 2 hours showed the greatest advance in sleep onset time (2.4 hours *vs*. 1.7 and 1.8 hours for the 30-minutes and 1-hour groups, respectively) [39]. Similarly, in another study, melatonin was administered 5.75 hours before the habitual bedtime, and 3,000 lux of intensive light was given 3 hours before the habitual waking up time, with the results showing that bright light plus melatonin was more effective than either treatment alone [40].

3.6.2. Chronotherapy

First reported by Czeisler and colleagues, chronotherapy is a method used to reset the circadian rhythms and thereby restore the normal circadian clock in DSWPD patients [41]. The strategy involves gradually postponing their time to fall

Table 1. Common treatments for circadian rhythm sleep-wake disorders.

Circadian Rhythm Sleep-wake Disorders	Common Treatment
Delayed sleep-wake phase disorder	1. Chronotherapy: Adhere to a fixed sleep schedule 2. Photic treatment: Morning bright light and avoiding light at nightfall or in the evening 3. Evening melatonin 4. Cognitive-behavioral therapy 5. Other treatments: Aripiprazole, nocturnal exercise, altering sleep habits
Advanced sleep-wake phase disorder	1. Chronotherapy: Adhere to a fixed sleep schedule 2. Photic treatment: Evening bright light 3. Other treatments: Health education and behavioral guidance
Non-24-hour sleep-wake rhythm disorder	1. Without light perception: (1) Chronotherapy: adhere to a fixed sleep schedule; (2) evening melatonin 2. With light perception: (1) Photic treatment: morning bright light and avoiding light at nightfall or in the evening; (2) other treatments: tasimelteon**,** triazolam, methylcobalamin, and valproic acid
Irregular sleep-wake rhythm disorder	1. Photic treatment: Morning or evening bright light 2. Evening melatonin 3. Behavioral therapy 4. Combination therapy

asleep until the sleep-wake time is consistent with the traditional social schedule. Specifically, the patient is required to postpone going to bed or getting up for 3 hours, and then postponing it again for another 3 hours every 2~5 days until the ideal sleep schedule is reached; subsequently, this sleep schedule should be strictly followed. One case report on 5 adults with DSWPD (age: 24–37 years) [41] and a study involving adolescents with subclinical DSWPD have shown that this method elicits positive results [42]; however, no randomized controlled trial has been undertaken to date to evaluate the efficacy of time therapy on DSWPD patients. A large number of small studies have also reported on the success of time-varying therapy, which seems to be well tolerated in typical DSWPD patients [41, 43, 44]. Nevertheless, chronotherapy is widely thought to be impractical as it requires a significant time commitment by the patient and is not constrained by external environmental conditions during the treatment. One study reported that DSWPD developed into free-running CRSWDs in one patient following the sleep scheduling intervention [45].

3.6.3. Photic Treatment

Light is a zeitgeber of circadian rhythms. Studies have found that light interventions can alter the phase of the body's circadian rhythm and change its direction and amplitude according to time, intensity, spectral properties, and duration of the light signal [46–48]. Studies have also shown that morning light can advance, while evening light or light before bedtime can delay the phase of the circadian rhythm [49]. The effect of light is related to its intensity and duration. Additionally, attention should be paid to individualization in clinical application. A phase response curve (PRC) has been generated to describe the magnitude and direction of the phase shift of the circadian rhythm according to the time, duration, and intensity of light exposure [49]. It is difficult to estimate the optimal time of light exposure based on the habitual sleep-wake time because the timing of the core body temperature minimum (CBTmin) has a large degree of interindividual variability relative to the time of the sleep-wake cycle [25]. Consequently, a circadian rhythm assessment should be undertaken before light treatment to ensure the best results. According to the light PRC, light has the greatest phase-advancing effect when administered shortly after CBTmin [50, 51]. Because the best source of light is natural light, patients are usually allowed to be exposed to sunlight for 30 minutes in the morning after waking up. When this is not possible, sitting next to a well-lit window will be the most effective. In the winter months, or for patients who do not have access to outdoor light, artificial bright light therapy can be used, and a variety of light boxes are available for this purpose [52]. The effects of treating DSWPD with different light wavelengths was recently evaluated, with early morning blue light (light-emitting diode, 470-nm peak wavelength, irradiance = 65 $\mu W/cm^2$) being found to exert a better effect on increasing the secretion time of endogenous melatonin and changing the waking up time, but not the sleep onset time [53]. An effective method for avoiding light at nightfall or in the evening may be to instruct patients to wear blue light-filtering goggles or glasses with amber lenses from sunset to bedtime [54]. The side effects of most light therapies (eye irritation, nausea, headache, dizziness, and excitement) are fairly mild and usually disappear over time. For patients with glaucoma, macular degeneration, cataracts, or diabetes-related eye conditions, light therapy may need to be performed under the guidance of an ophthalmologist [52].

3.6.4. Cognitive-behavioral Therapy

Adverse treatment results or recurrence are common after various DSWPD treatment programs [55, 56]. The overlap between DSWPD and insomnia is large, especially when patients try to go to bed earlier [16]. Consequently, interventions for insomnia, such as cognitive-behavioral therapy (CBT), may also affect the sleep delay of DSWPD patients [57]. Studies have shown that adolescents diagnosed with CRSD have many symptoms of cognitive insomnia [58]. Moreover, recent studies have reported that the combination of CBT and phototherapy has produced better long-term ef-

ficacy for adolescents and young patients with DSWPD [59, 60]. This suggests that patients with DSWPD may benefit from CBT for insomnia. Nevertheless, many issues remain to be resolved regarding CBT treatment for DSWPD, such as the number of treatment courses, how experienced the therapist should be, and the form of treatment. More clinical trials are needed to evaluate and perhaps improve the efficacy of CBT in the treatment of DSWPD.

3.6.5. Other Treatments

Aripiprazole (APZ) is a second-generation antipsychotic drug that acts as a partial agonist of both D_2 and serotoninergic 5-HT_{1A} receptors and as an antagonist of 5-HT_{2A} receptors [61]. Depression is the most common mental illness associated with DSWPD [62], and low-dose APZ is reported to be effective as an adjunct therapy in major depression [63]. In addition, low-dose APZ can prolong the total sleep time (TST) and advance the sleep-wake phase [64]. These observations indicate that this drug will likely become a new treatment option for patients with DSWPD. Several studies have shown that nocturnal exercise delays the circadian rhythm of the human body [65-67]. This finding may have particular relevance for many adolescents, and young people who undertake physical activities such as part-time work, exercise, and social activities before going to bed, as doing so may increase their risk of DSWPD. Other treatment options, such as health education and behavior guidance, will also reduce the delay of the circadian rhythm. It is recommended to patients that they reduce their bad sleeping habits (such as using electronic devices in bed and drinking alcohol or coffee after 16:00 hours) and develop good sleep habits (*e.g.*, go to bed when sleepy) [68, 69].

4. ADVANCED SLEEP-WAKE PHASE DISORDER

4.1. Definition

Advanced sleep-wake phase disorder (ASWPD), also known as advanced sleep phase syndrome, is a relatively rare circadian rhythm sleep disorder. It is mainly manifested in an individual's main sleep period, during which sleep onset and wake times usually occur at least 2 hours earlier than the societal norm compared with normal individuals [70]. Patients with ASWPD usually fall asleep from between 6 and 9 in the evening and wake up from between 2 and 5 in the morning. The main complaints include drowsiness and difficulty in staying awake in the evening, waking up before dawn, and difficulty falling asleep after waking up often referred to as the "nightingale" chronotype [71]. Unlike other sleep maintenance disorders, early morning awakenings occur after a normal period of undisturbed sleep, that is, the sleep cycle is normal for the age. In addition, unlike excessive sleepiness due to other reasons, the daytime work or learning ability of people with this disorder is not affected by sleepiness. However, because affected people fall asleep much earlier than what is considered normal, activities in the evening are usually shortened [12].

4.2. Epidemiology

The prevalence of ASWPD is much lower than that of DSWPD, possibly because ASWPD has little impact on daytime functioning, learning, work, and social activities, such that patients rarely seek medical advice. The prevalence of ASWPD is estimated to vary from 1% to 7% according to the different populations evaluated, while the overall prevalence is higher in men and the elderly [17]. A large survey of a middle-aged and elderly population (40~64 years old) showed that the prevalence of ASWPD was approximately 1%, and increased with age; however, no gender differences were found [72]. In a multi-center survey of 9,000 elderly people aged 65 years and older, early waking was reported by 20% of participants [73].

4.3. Etiology

The etiology of ASWPD is unclear. In recent years, numerous studies have reported that ASWPD has a strong heritability component. Familial studies have suggested that it displays an autosomal dominant pattern of inheritance, while one variant of ASWPD has been associated with a mutation in the circadian clock gene *PER2* [74]. Familial ASWPD has been reported to result in a shorter circadian rhythm cycle, leading to an earlier circadian rhythm [75]. Mutations in the casein kinase I delta gene *(CKIδ)* have also been reported to lead to a shorter physiological cycle [76]. A missense mutation in the human cryptochrome 2 *(CRY2)* gene was also identified in a study on familial ASWPD [77]. In addition, behavioral factors may also play a role. If an individual receives less light in the afternoon or evening, or is prematurely exposed to morning light following early awakening, the circadian rhythm can be advanced, leading to an increased risk of an early sleep phase [78].

4.4. Diagnostic Evaluation

The diagnosis of ASWPD is mainly based on clinical symptoms. A sleep diary and actigraphy are two established methods for determining ASWPD. Both methods should record at least 7 consecutive days (including rest days), but preferably 14 days [79]. The MEQ can provide further diagnostic value for ASWPD, with most patients presenting with ASWPD being rated as "early morning type" [80]. Determining the timing of DLMO, a circadian rhythm marker, can identify an advance in the circadian rhythm phase, especially in cases of familial ASWPD [80]. When it is necessary to distinguish between ASWPD and other types of sleep disorders, a PSG examination can be performed. If the patient is allowed to sleep according to his wishes, the PSG results show a normal sleep structure. If the patient is required to sleep on the traditional sleep schedule, however, PSG results show that the sleep latency is shortened while both TST and rapid eye movement sleep are reduced. PSG is not currently used as a routine diagnostic method for ASWPD [12].

4.5. Diagnostic Criteria

The diagnosis of ASWPD requires that the following five main criteria are met [12]: 1) There is an advance (occurs earlier) in the phase of the major sleep episode in relation to the desired or required sleep onset and wake-up times, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening; 2) symptoms are present for at least 3 months; 3) when patients are allowed to sleep in accordance with their internal biological clock, sleep

quality and duration are improved with a consistent but advanced timing of the major sleep episode; 4) sleep logs and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days), including work/school days and free days, demonstrate a stable advance in the timing of the habitual sleep period; and 5) the sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

4.6. Treatments

The treatment recommendations are shown in Table **1**.

4.6.1. Melatonin Treatment

In theory, melatonin can delay the circadian rhythm phase, which can delay the sleep onset time of patients with ASWPD. According to the melatonin PRC, to delay the circadian rhythm phase of ASWPD, melatonin should be given in the early morning. However, there is a lack of clinical data and information regarding the safety and effectiveness of melatonin [81]. In addition, melatonin has a sedative and hypnotic effect, so taking melatonin in the morning may make it difficult to stay awake, making it more difficult for individuals to stick to the scheduled sleep and wake-up times [82]. Accordingly, the American Medical Association does not currently recommend taking melatonin or melatonin agonists in the morning to treat ASWPD [36]. The side effects of melatonin at low doses (0.5~5.0 mg), which include headache, nausea, dizziness, and drowsiness, are often mild [83].

4.6.2. Chronotherapy

The purpose of chronotherapy is to reschedule the rest schedule. The time to fall asleep and get up is gradually shifted backward, *i.e.*, the sleep onset time is delayed by 3 hours every 2 days until the sleep time is consistent with the desired later bedtime. In one case study in which a patient with ASWPD was instructed to go to bed 3 hours earlier every 2 days until reaching the goal of falling asleep at 23:00 hours, the 5-month follow-up after treatment showed that the patient could maintain a bedtime of 23:00 hours and a waking up time of 07:00 hours. Notably, this patient had mild obstructive sleep apnea, but did not specify whether or not it had been treated. Having this information would have been very useful for fully understanding the effect of chronotherapy treatment. Further studies are needed to support the use of time therapy for the treatment of ASWPD [44].

4.6.3. Phototherapy

The occurrence of ASWPD is related to the early phase of melatonin secretion. Consequently, exposure to bright light every night can delay the phase of melatonin secretion, thereby delaying sleep. Phototherapy is usually performed between 19:00~21:00 hours, which can improve sleep efficiency and delay the circadian rhythm [84]. However, the intensity of the light applied is currently not uniform across studies. A patient was given 2,500 lux of bright light irradiation at night and continued treatment for 17 months such that the sleep phase returned completely to normal, an effect that could subsequently be maintained by only sporadic bright light application [85]. The latest AASM guideline recommends the use of night bright light therapy in the treatment of ASWPD [36]. To delay the circadian rhythm time, it is recommended that individuals are exposed to at least 5,000 lux of bright light at night for 2 hours [86]. Multiple studies have shown that the circadian rhythm phase is delayed in elderly patients exposed to bright light at night; however, these patients reported that they could not tolerate light, which resulted in poor compliance [87, 88]. Palmer and colleagues found that compared with patients receiving enhanced intensity bright light treatment in the evening, those who received dim light treatment were more compliant, and their symptoms also improved [88]. The side effects of phototherapy, which include eye fatigue, nausea, restlessness, and headaches, are minimal and usually disappear spontaneously [89, 90].

4.6.4. Other Treatments

Health education and behavioral guidance can be given to patients, including the avoidance of bright light in the morning, taking a nap at noon, trying to postpone bedtime at night, performing physical activities, and walking in the evening under bright light. Any possible anxiety or frustration should be treated. In addition, no study has assessed the use of hypnotic drugs and CBT as adjuvant therapy for ASWPD.

5. NON-24-HOUR SLEEP-WAKE RHYTHM DISORDER

5.1. Definition

Non-24-hour sleep-wake rhythm disorder (N24SWD), also known as free-running type sleep disorder, over 24 hours of sleep-wake syndrome, or non-induced sleep-wake syndrome, is a type of sleep disorder characterized by a chronic and stable sleep-wake pattern [12]. The characteristics are mainly the long-term, constant l–2-h delay in the time to fall asleep and awaken, which cannot be disrupted or affected by a natural and social exogenous 24-h cycle. When a patient tries to follow the traditional sleep-wake time, insomnia, daytime sleepiness, or both will occur; however, when the patient's sleep-wake time is consistent with the light and dark cycle and social activities, the sleep quality and duration are normal [91]. Consequently, the patient may alternate between symptomatic and asymptomatic phases. When the patient tries to establish a consistent, traditional sleep–awakening time for reasons of study or social activities, they have to force themselves to awaken from the sleep phase (sleep deprivation). Over time, this will aggravate the symptoms of insomnia or daytime sleepiness, leading to the occurrence of physical symptoms such as dizziness, headache, fatigue, and emotional disturbances, such as cognitive impairment.

5.2. Epidemiology

N24SWD is very rare in the general population and is more common in blind people. It is estimated that approximately 50% of blind people have N24SWD, while 70% have chronic sleep disorders; thus, N24SWD is also called blind sleep patterns [92]. A questionnaire survey on the sleep problems of blind people found that sleep problems are more frequent in blind people than in sighted people (83% *vs*. 57%), while 18% of blind people exhibit a periodic pattern of sleep-wake disturbance compared with 8% for sighted people [93]. The onset of N24SWD does not occur only

when vision is lost. N24SWD may also occur in individuals with congenital blindness and adults with complete vision loss, sometimes after many years. In a large case series of sighted people with N24SWD (57), 72% were men, and most first showed symptoms in their teens or twenties. Similar to DSWPD patients, those with N24SWD seem to have greater comorbidity of psychiatric disorders, with 28% displaying premorbid mental disorders before N24SWD symptom onset, and another 34% exhibiting symptoms of severe depression after the appearance of N24SWD symptoms [91]. In a recent study investigating blind female patients with or without light perception, the incidence of N24SWD was reported to be as high as 63% [94]. Little is known about the prevalence of N24SWD in children or adolescents, and its natural process has not been described.

5.3. Etiology

N24SWD patients without light perception may show a completely free-running endogenous circadian rhythm due to a lack of light zeitgeber input into the SCN [91]. Importantly, if blindness is due only to an outer retinal (cones and rods) disease and the function of the photosensitive retinal ganglion cells and the hypothalamic pathway of the retina are still preserved, the circadian rhythm can still be synchronized with the outside environment [95]. This explains why not all blind people have N24SWD. However, the pathogenesis of N24SWD in sighted patients remains unclear. Possible reasons include reduced light exposure, reduced sensitivity to light, or reduced social and physical activity. An abnormal sleep-wake rhythm can be induced or aggravated by changes in sleep habits (night-shift work, unemployment), social isolation, and physiological factors that cause behavioral changes. Several studies have found that patients with mental illness (such as depression or personality disorder) can still develop N24SWD due to social time suggestive factors change or eliminate [91].

5.4. Diagnostic Evaluation

The diagnostic criteria for N24SWD mainly include sleep disturbance, daytime symptoms, and disruptions in work and daily life. Patients may present different main complaints that range from insomnia or early waking to excessive daytime sleepiness. A detailed medical history, a sleep diary, and actigraphy are essential for diagnosis. A sleep diary and actigraphy covering 14 days can show that a patient's sleep-wake rhythm cycle is prolonged daily, representing a lack of stability between the patient's sleep-wake cycle and the 24-hour light-dark cycle [12]. In addition, the continuous measurement of DLMO as a circadian rhythm marker can indicate a change in DLMO timing over time can also help N24SWD diagnosis [80]. MEQ has little application value for N24SWD, while PSG is mainly used for differential diagnosis and the elimination of other types of sleep disorders, not as a routine examination.

5.5. Diagnostic Criteria

The diagnosis of N24SWD requires that the following four main criteria are met [12]: 1) There is a history of insomnia, hypersomnia, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-h light-dark cycle and the non-entrained, endogenous circadian rhythm of sleep-wake propensity; 2) symptoms persist for at least 3 months; 3) daily sleep logs and actigraphy for at least 14 days, preferably longer for blind people, demonstrate a pattern of sleep onset and wake times that typically delay each day, with a circadian period that is usually longer than 24 h; 4) the sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

5.6. Treatments

The purpose of N24SWD treatment is to reconstruct a stable 24-hour sleep-wake rhythm consistent with the external environment, thereby improving sleep quality and daytime function. The recommendations for N24SWD treatment depend on the light perception of the patient (Table **1**). For N24SWD patients without light perception, only non-photoinduced methods can be used to adjust the circadian phase of sleep. The treatments mainly use sleep hygiene education, adjusted sleep time, and melatonin treatment. Specifically, these treatments aim to educate patients on how to adjust their sleep and re-establish a sleep-wake schedule synchronized with the external environment, society, and their occupation, to improve the circadian rhythm. According to the 2015 AASM guideline, melatonin therapy is recommended for blind people with N24SWD [36]. In addition, tasimelteon, a selective agonist of the melatonin receptors MT1 and MT2, was the first medication approved by the US Food and Drug Administration in 2014 for the treatment of N24SWD. Tasimelteon is safe and well-tolerated for long periods, and is not associated with withdrawal or dependency symptoms [96]. For the blind, some studies have shown that taking a low dose of melatonin (ranging from 10 mg [97] to 0.5 mg [98]) at a fixed time, *i.e.*, approximately 1 hour before the desired bedtime, can effectively guide and improve sleep. For people with normal sight, light exposure can be used to enhance the light and dark cycles, and/or melatonin can be administered to regulate circadian rhythms. In a case report of a sighted woman with free-running sleep-wake and melatonin rhythms, the entrainment effect was achieved by performing conventional bright light treatment for 2 hours immediately after waking up [99]. In another individual, a 24-hour melatonin profile was restored after entrainment with a combination of bright morning light for 2 hours, bright light avoidance before bedtime, and strict darkness while sleeping [100]. In a separate case, a sighted patient with N24SWD received a 3-hour-long morning light therapy, and PSG results showed an improvement in the 24-hour sleep pattern of the patient [101]. Meanwhile, a combination of light and melatonin treatment has also been tried. Although long-term compliance is often challenging, some initial successes have been achieved [102]. Yanagihara *et al.* reported that the symptoms of two sighted patients with N24SWD were improved by tasimelteon (8 mg at 20:00 hours) and triazolam or methylcobalamin combination therapy [103]. Moreover, the sleep-wake rhythm of an N24SWD woman with depressive symptoms was restored to a 24-hour pattern when taking low-dose valproic acid, and her depressive symptoms also tended to improve as a result of synchronization without antidepressant medication. Low-dose valproic acid appears to be an effective means of enhancing the circadian rhythm in patients with N24SWD and may also improve related depressive symptoms; however, its specific

safety remains to be explored [104]. Overall, N24SWD patients with or without sight must have good compliance and adhere to treatment, or they may easily relapse.

6. IRREGULAR SLEEP-WAKE RHYTHM DISORDER

6.1. Definition

Irregular sleep-wake rhythm disorder (ISWRD), also known as no circadian rhythm, grossly disturbed sleep-wake rhythm, and chaotic sleep-wake rhythm, manifests as a disordered sleep-wake cycle that shows no clear pattern. In the 24-hour cycle, the sleep-wake phase can be divided into 3 or more additional phases, with each phase lasting from between 1 to 4 hours. As a result of disturbed night sleep maintenance and an increase in daytime napping, patients often complain of night insomnia or excessive daytime sleepiness. Relative to age, the individual TST is normal, whereas the biological clock is out of balance. Twenty-four-hour PSG records frequently indicate short sleep periods, reduced sleep spindles, and reduced or absent non-rapid eye movement sleep [105].

6.2. Epidemiology

Although the incidence of ISWRD in the general population is unknown, it is estimated to be very low [106]. The disease can occur in any population, and there is no known gender difference. However, this disease is more common in the elderly, especially in those with age-related neurological diseases such as dementia. A few individuals with normal cognitive functions, but irregular work and rest schedules, long-term bed rest, or who frequently doze off, and especially those who lack a regular life, are more susceptible to this disorder. ISWRD can also be seen with brain trauma and in children with mental retardation [80, 107].

6.3. Etiology

The etiology of ISWRD is not well understood, and many factors may contribute to its development. Poor sleep hygiene (such as in people with extremely irregular lives) and the lack of a zeitgeber (lack of light, exercise, and social cues) can induce or worsen the development of ISWRD [108]. Elderly people in nursing homes and patients with dementia tend to be less exposed to outdoor light and participate in fewer social activities, and also suffer vision loss and age-related SCN changes. These factors are speculated to be related to the occurrence and maintenance of ISWRD [109, 110]. ISWRD symptoms have also been found in people with Angelman syndrome and Williams syndrome. The concentration of melatonin and its metabolites in these patients was reported to decrease at night and increase during the day, except for the abnormal melatonin rhythm, and its amplitude is also significantly reduced. This may be related to polymorphism in melatonin synthesis pathways or mutations in the genes encoding melatonin receptors [111, 112].

6.4. Diagnostic Evaluation

The most useful methods currently available for the evaluation of ISWRD are the sleep diary and actigraphy, both of which can show whether a patient lacks a clear sleep-wake circadian rhythm. ISWRD mainly manifests as multiple irregular sleep-wake episodes within 24 hours. If possible, patients should be continuously monitored for 14 days. For patients with cognitive impairment, however, the objectivity of the evaluation method is affected to a certain extent [80]. Although 24-hour PSG can assess sleep-wake patterns, it is not routinely used. There is insufficient evidence regarding the use of DLMO and MEQ for the diagnostic evaluation of ISWRD. Importantly, this sleep disorder must be distinguished from other sleep disorders.

6.5. Diagnostic Criteria

The diagnosis of ISWRD requires that the following four main criteria are met [12]: 1) The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24 hours, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both; 2) symptoms are present for at least 3 months; 3) sleep logs and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days), demonstrate no major sleep period and multiple irregular sleep bouts with at least three brief sleep periods during 24 hours; and 4) the sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

6.6. Treatments

The main goal of ISWRD treatment is to consolidate night sleep and maintain daytime wakefulness by enhancing the intensity of the endogenous circadian rhythm to make it consistent with the circadian rhythm of the external environment (Table **1**).

6.6.1. Melatonin

Melatonin is currently used as a treatment for ISWRD. For children and adults with psychomotor retardation, melatonin at a dose of 2~20 mg can improve and consolidate sleep patterns and reduce daytime sleep [113]. Similarly, taking 2 mg of melatonin before going to bed can improve the sleep of patients with schizophrenia [114]. In the treatment of patients with Angelman syndrome and ISWRD, the administration of 1 mg of melatonin between 18:00 and 19:00 hours significantly increases sleep time at night compared with that in the daytime [111]. A large-scale randomized controlled trial showed that light could improve cognitive function in people with dementia while melatonin shortens the sleep onset latency, causing depression in the elderly; however, melatonin combined with phototherapy improves sleep efficiency [115]. In the elderly, therefore, phototherapy or phototherapy combined with melatonin therapy is recommended, whereas melatonin treatment alone is not.

6.6.2. Phototherapy

Bright light exposure is used to strengthen the light-dark cycle. Strong daytime light exposure can reduce daytime napping, consolidate nighttime sleep, and ultimately improve the circadian rhythm of sleep and wakefulness in patients. There is evidence that ISWRD patients with dementia receiving strong light exposure for 2 hours (3,000~5,000 lux) every morning for more than 4 weeks have fewer daytime naps and increased nighttime sleep time [116]. Additionally, exposure to bright light, either in the morning or evening, is beneficial for Alzheimer's disease patients. Bright lights in the morning (2,500 lux) have been shown to increase noctur-

nal sleep time by 20~30 minutes, while bright lights at night have been shown to improve rest-activity rhythms [117]. Similarly, bright morning light (4,500 lux) treatment was shown to normalize the sleep-wake pattern of approximately half of a small group of children with neurodevelopmental delay [118].

6.6.3. Behavioral Therapy

Patients should be encouraged to perform appropriate physical activities and exercises during the day to increase the amount of outdoor light they receive. During the treatment period, patients need to be urged to strictly abide by the work-rest schedule. Even when sleepy and fatigued, a patient should try his best to stay awake during the prescribed awakening period and gradually adjust and establish the regular sleep-wake cycle [36, 105].

6.6.4. Combination Therapy

When a single treatment is not effective, combined treatments can be used, such as combining phototherapy with behavioral intervention (regular exercise, adjusting sleep time, reducing night light exposure, and reducing night noise) [106]. A combination of phototherapy, time therapy, and drug therapy (vitamin B_{12} and sedative-hypnotics) elicited a 45% success rate [119]. Therefore, the treatment of such patients should be individualized. For elderly patients, however, any adverse conditions, especially mental states, should be closely monitored during medication.

CONCLUSION

CRSWDs encompass a wide spectrum of disorders, all of which are associated with the dysregulation of the internal circadian system with respect to the external environment. This dysregulation can have a significant impact on physical and mental health, and there is a high comorbidity of psychiatric disease with many of these disorders. This review provided an update on recent findings and developments related to the epidemiology, etiology, diagnostic evaluation, diagnostic criteria, and treatment of CRSWD. This understanding has promoted the application of basic research on biological rhythms in clinical sleep medicine practice. For instance, the measurement of biomarkers of endogenous biological rhythms has become a clinical diagnostic method, while the restoration of normal biological rhythms has become the goal of clinical treatment. We believe that further in-depth research on circadian rhythms will lead to the identification of new research directions and better solutions for problems related to sleep disorders. It is foreseeable that the development of new drugs to treat CRSWDs will be targeted toward sleep- and wake-promoting signals of the biological clock.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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