

**Treatment guidelines for Circadian Rhythm Sleep
– Wake Disorders of the Polish Sleep Research Society
and the Section of Biological Psychiatry of the Polish
Psychiatric Association.
Part II. Diagnosis and treatment**

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Summary

Aim. Circadian rhythm sleep-wake disorders (CRSWD) are a group of disorders, in which the timing of sleep and wakefulness significantly differs from a patient's expectations or socially acceptable times. The aim of the article is to present the current principles for the diagnosis and treatment of CRSWD in adults and children.

Method. Guidelines proposed as CRSWD treatment standard are based on the recommendations from the scientific societies involved in the sleep research and medicine. Researchers participating in the guidelines preparation were invited by the Polish Sleep Research Society and the Section of Biological Psychiatry of the Polish Psychiatric Association based on their significant contribution to the circadian rhythm research and/or clinical experience in the treatment of these disorders. Finally, the guidelines were adjusted to the questions and comments given by the members of both Societies.

Results. Patients with endogenous CRSWD are often misdiagnosed and treated for insomnia or hypersomnia. Therefore, each patient reporting sleep-wake disorders should

be interviewed about the quality of sleep and its timing during free days (e.g. weekends, holidays). A valid CRSWD diagnosis can be also established by using sleep diaries/logs and actigraphy. The treatment of choice for CRSWD is chronotherapy, which involves melatonin application, light therapy, and behavioral interventions. Sleep disorders associated with shift work and time zone changes are a growing health problem. Interventions for these disorders should primarily focus on prevention.

Conclusions. The main problem in the treatment of CRSWD is an invalid diagnosis. Hypnotics and/or psychostimulants are often used instead of chronotherapeutic interventions, what can alleviate symptoms but is not an effective treatment.

Key words: circadian sleep-wake rhythm disorders, diagnosis, treatment

Abbreviations:

ASWPD – advanced sleep-wake phase disorder
CNS – central nervous system
CRSWD – circadian rhythm sleep-wake disorders
DLMO – dim light melatonin onset
DSWPD – delayed sleep-wake phase disorder
ICSD-3 – International Classification of Sleep Disorders
ISWRD – irregular sleep-wake rhythm disorder
N24SWRD – non-24-hour sleep-wake rhythm disorder
SWD – shift work disorder

Introduction

Circadian rhythm sleep-wake disorders (CRSWD) are a group of sleep disorders of endogenous or exogenous origin. Endogenous disorders include delayed sleep-wake phase disorder (DSWPD), advanced sleep-wake phase disorder (ASWPD), non-24-hour sleep-wake rhythm disorder (N24SWRD), and irregular sleep-wake rhythm disorder (ISWRD). Exogenous disorders include shift work disorder (SWD) and jet lag disorder (time zone change disorder).

In endogenous disorders, sleep periods occur at times congruent with the patient's internal biological rhythm but are socially unacceptable or inconvenient, which is the essential feature of these disorders. In exogenous disorders, sleep periods are not synchronized with the patient's internal biological rhythm, while their timing is driven by working hours or a rapid change of time zones. Both groups of disorders are related to sleep and wake disturbances, and their long persistence leads to a severe impairment in physical health and social functioning.

The aim of this article is to provide the recommendations for the diagnosis and treatment of CRSWD, as a continuation of the first part of the guidelines, in which the physiology of the circadian rhythm and its assessment standards were presented, along with the recommendations for the use of chronobiological therapeutic methods [1].

Method

This article is based on the lectures delivered by a group of experts during two sessions of the 9th Congress of the Polish Sleep Research Society in Gniezno, April 2016. The guidelines contain proposed standards of CRSWD treatment based on the analysis of recommendations published by other scientific societies [2–4], the Third Edition of the International Classification of Sleep Disorders – ICSD-3 [5], and the authors' opinions. Participants of this panel were the scientists with significant contributions in circadian rhythm research and/or many years of clinical experience in the treatment of such disorders invited by the Boards of the Society and the Section. In addition, the final version of the guidelines was substantially adapted to the questions from participants of the above-mentioned convention and comments given to the standards initial version by the members of the Society and the Section.

Guidelines for treatment of endogenous circadian rhythm sleep-wake disorders

Endogenous CRSWD are a group of sleep disorders in which patients typically complain about insomnia symptoms occurring during their preferred sleep times or the excessive sleepiness when they want to stay awake. These complaints may also be present despite normal sleep quality and duration. They are caused by a discrepancy between biologically preferred sleep periods (i.e., time to bed, time out of bed) and the patient's or social expectations. Despite some similarities with insomnia or excessive sleepiness, the mechanism of CRSWD is different. In insomnia or excessive sleepiness, the "dysfunction" is related to the excitatory and inhibitory systems in the brain, while in CRSWD the source of the problem is a discrepancy between the functioning of the biological clock and social timing.

Furthermore, endogenous CRSWD should be distinguished from the exogenous CRSWD – related to shift work, irregular lifestyle, or rapid time zone changes (i.e., jet lag). Unfortunately, in clinical practice this classification is not necessarily unequivocal. Typically, patients have a genetically-driven extreme evening ("owl") or morning ("lark") chronotype, which determines their preferred late or early bedtime and activity periods. The early or late activity periods additionally affects the biological clock phase shift, in relation to the commonly occurring sleep times. The problem of extreme chronotype concerns mainly the patients with DSWPD and ASWPD. General criteria for the diagnosis of circadian rhythm disorders, according to the ICSD-3, are presented in Table 1 [5].

Table 1. General diagnostic criteria for circadian rhythm sleep-wake disorders, according to the International Classification of Sleep Disorders – ICSD-3

For the diagnosis of CRSWD the three following criteria must be met:	
A.	A chronic or recurrent pattern of the sleep-wake rhythm disruption primarily due to the alteration of endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environment or social/work schedules
B.	The circadian rhythm disruption leads to insomnia, excessive sleepiness, or both
C.	The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning

Delayed sleep-wake phase disorder (DSWPD) is the most common disorder of circadian rhythm. The prevalence of this disorder is between 7% and 16% among adolescents and young adults. Approximately 10% of patients with persisting sleep-onset insomnia, in fact suffer from DSWPD. The exact prevalence of DSWPD in the general population is not precisely known. It is characterized by a delayed sleep-wake rhythm, usually more than two hours compared to the common or socially acceptable sleep times. Patients with this disorder usually complain of evening arousal, delayed sleepiness, difficulty to wake up in the morning, and fatigue on the weekdays. The delayed sleep pattern usually starts at the age of 18–20 years, although cases of an early childhood onset are also reported. When untreated, the delayed sleep pattern can persist for years, although the symptoms usually decrease with age. The difficulties, however, can increase in the autumn and winter seasons.

In order to successfully manage school or work activities, some patients with DSWPD use various substances and hypnotics in the evening and psychostimulants during the day, which can reinforce disturbed sleep rhythm. During holidays/days off, when a patient is allowed to follow his/her preferred schedule, sleep difficulties and daytime sleepiness are not present. Approximately 40% of patients with DSWPD have family members with similar problems. The association of DSWPD with polymorphisms of some clock genes, mainly PER3 and CLOCK, has been demonstrated [6]. Regardless of the endogenous and biological basis, the delayed sleep pattern can be also induced by an extended late night activity, along with avoiding activity during the day (sometimes as a symptom of school phobia or social anxiety disorder). The ICSD-3 criteria for diagnosis of DSWPD and other endogenous CRSWD are presented in Table 2.

Table 2. Diagnostic criteria for endogenous circadian rhythm sleep-wake disorders according to the International Classification of Sleep Disorders – ICSD-3

<p>Delayed sleep-wake rhythm disorders (DSWPD)</p>	<p>A–E criteria must be met:</p> <p>A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake up time, or a chronic or recurrent inability to fall asleep and difficulty awakening at the desired or required clock time, as evidenced by complaint by the patient or caregiver.</p> <p>B. The symptoms are present for at least three months.</p> <p>C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24-hour sleep-wake pattern.</p> <p>D. Sleep log and, whenever possible, actigraphy monitoring for at least seven days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days (especially without using an alarm clock) must be included within this monitoring.</p> <p>E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.</p>
<p>Advanced sleep-wake phase disorder (ASWPD)</p>	<p>A–E criteria must be met:</p> <p>A. There is advance (early timing) of the major sleep episode in relation to the desired or required sleep time and wake up time, as evidenced by a chronic or recurrent complaints of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time of awakening.</p> <p>B. Symptoms are present for at least three months.</p> <p>C. 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.</p> <p>D. Sleep log and, whenever possible, actigraphy monitoring for at least seven (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.</p> <p>E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.</p>

table continued on the next page

<p>Irregular sleep-wake rhythm disorder (ISWRD)</p>	<p>A–D criteria must be met:</p> <p>A. The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both.</p> <p>B. Symptoms are present for at least three months.</p> <p>C. Sleep log and, whenever possible, actigraphy monitoring for at least seven days (preferably 14 days), demonstrate no major sleep period and multiple, irregular sleep bouts (at least three) during a 24-hour period.</p> <p>D. The sleep disturbances are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.</p>
<p>Non-24-hour sleep-wake rhythm disorder (N24SWD)</p>	<p>A–D criteria must be met:</p> <p>A. There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.</p> <p>B. Symptoms persist over the course of at least three months.</p> <p>C. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day (less often there is advance).</p> <p>D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.</p>

Chronobiological treatment of DSWPD involves the gradual advance of wake-up time (e.g., wake-up half an hour earlier each week). Alternatively, the bedtime can be delayed (i.e., moved “for later”) each night for 1–3 hours until reaching the desired sleep onset and offset. Behavioral shifting of sleep times to earlier hours should be accompanied by an exposure to bright light after waking up (light therapy), and further strengthened by melatonin administration several hours before the bedtime. Table 3 presents the recommended timing of melatonin and light therapy administration, depending on the patient’s typical hours of sleep periods and results on the MEQ and CSM chronotype questionnaires.

Table 3. Recommended times of melatonin and light therapy administration in the treatment of delayed sleep phase, depending on the patient's typical hours of sleep period and the results on the MEQ and CSM chronotype questionnaires

	Sleep onset	Sleep offset	Mid-sleep	MEQ result	CSM result	Melatonin administration time	Beginning of the light therapy
Definite evening chronotype	2:00–3:00	10:00–11:30	6:00–7:00	23–26	13–14	22:15	08:15
				27–30	15–16	22:00	08:00
Moderate evening chronotype	0:45–2:00	8:30–10:00	4:45–6:00	31–34	17–18	21:45	07:45
				35–38	19–21	21:30	07:30
				39–41	22–24	21:15	07:15
Intermediate chronotype	22:45–0:45	6:30–8:30	2:30–4:45	42–45	25–28	21:00	07:00
				46–49	29–32	20:45	06:45
				50–53	33–37	20:30	06:30
				54–57	38–42	20:15	06:15

Melatonin treatment is the most effective in the sleep-wake rhythm advancement when applied at least 6 hours before mid-sleep on free days. Bright light therapy advances a sleep-wake rhythm the most when applied in the second half of the sleep period (there is a need to wake the patient up), no later than 5 hours after MSF. Details of the therapeutic intervention principles, including the dosage of melatonin, are described in the first part of the guidelines [1].

Advanced sleep-wake phase disorder (ASWPD) is characterized by an earlier timing of sleep onset and offset, occurring several hours prior to the common or desired sleep times. The exact prevalence of ASWPD in the general population is not exactly known. Approximately 1% of middle-aged adults and elderly people are estimated to be suffering from this disorder. It usually begins in middle age (although early onset in childhood is occasionally reported), and lasts for many years. The familial pattern of ASWPD, associated with PER2 gene polymorphism, was also reported. The main symptoms are: a tendency to fall asleep early in the evening, fatigue during the day, especially in the late afternoon and evening, and early morning awakening. These disturbances are likely to increase in the autumn and winter season. The treatment involves behavioral therapy (delaying bedtime gradually), often together with chronotherapy (e.g., light therapy before sleep, melatonin administration in the morning). However, treatment with melatonin in patients with ASWPD is not as effective as in other CRSWD. Additionally, early morning melatonin administration can cause sleepiness after the planned time of waking up.

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by the lack of a clearly defined circadian sleep-wake rhythm. In general, there are several (at least three) sleep episodes during the day, as well as periods of sleep and wakefulness randomly occurring at different times of the day. In addition, patients or their caregivers commonly complain about insomnia or excessive daytime sleepiness. ISWRD is more

commonly observed in patients with organic lesion of CNS (typically Alzheimer's disease), and in children with neurodevelopmental disorders.

In non-24-hour sleep-wake rhythm disorder (N24SWD), the intrinsic circadian pacemaker is not synchronized to a 24-hour cycle; the non-24-hour period can be longer (or, less often, shorter) than 24 hours. Therefore, patients' sleep onset and offset are constantly delayed, typically manifested as recurrent episodes of difficulty falling asleep at night or excessive sleepiness during the day. This disorder affects mainly blind people who are unable to perceive light (e.g., after enucleation), which can be diagnosed by an examination of the pupillary reflex. The exact prevalence of N24SWD in the general population is unknown, however, according to various authors it occurs in approximately 40 to 70% of blind individuals who do not react to light.

For the treatment of irregular and non-24-hour circadian rhythm disorders, apart from the methods of synchronizing the circadian rhythm: light therapy (with the exclusion of blind people) and melatonin, it is important to note that patients should also regularly engage in everyday activities and avoid naps during the day.

Guidelines for the treatment of exogenous circadian rhythm sleep-wake disorders: disorders associated with shift work and time zone changes (jet lag)

Exogenous CRSWD are an increasingly frequent reason for seeking medical advice. In industrialized countries, nearly 20% of professionally active individuals are employed in a job that requires shift work, irregular or unconventional working hours. Approximately 10 to 40% of such individuals experience sleep-wake disturbances, called shift work disorder (SWD). SWD prevalence in the general population is estimated to be 2 to 5%. Jet lag disorder results from a rapid change of time zones. The number of traveling people is constantly increasing, but there is no precise data on the prevalence of jet lag disorder. Among airline crews of two US companies, 33.7% of individuals reported sleep disorders which were 3.7 times more likely in men and 5.7 times more likely in women, compared to the general population adjusted for age [7].

Disorder associated with shift work

For the diagnosis of SWD the following criteria must be met:

- A. There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time of sleep.
- B. The symptoms must have been present and associated with a shift work schedule for at least three months.
- C. Sleep log and actigraphy monitoring (whenever possible and preferably with concurrent light exposure measurement) are measured for at least 14 days (work and free days) that demonstrate a disturbed sleep and wake pattern.

- D. The sleep and/or wake disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.

The basic method of SWD diagnosis includes a patient interview and an assessment of his/her sleep-wake rhythm using sleep logs and actigraphy. Usefulness of clinical rating scales, such as the MEQ, and biological markers of circadian rhythm: DLMO, core body temperature, 6-sulfatoxymelatonin in urine, is low [3]. Isolated studies had shown that individuals with morning chronotype according to the MEQ adapt worse to night shift work and experience more sleepiness, compared to individuals distinguished with evening chronotype [8]. Other studies, however, did not confirm such a relationship between MEQ results and shift work adaptability [9].

In addition to the sleep-wake rhythm assessment, other negative consequences of shift work in patients with SWD should be evaluated. Shift work increases the risk of somatic diseases, especially gastrointestinal tract disorders (gastric and duodenal ulcers), cardiovascular disorders (hypertension, arrhythmias and ischemic heart disease), endocrine disorders (e.g., menstrual cycle disorders in women), metabolic disorders (overweight/obesity, type II diabetes), as well as mood and emotion regulation disorders (irritability, higher risk of depression). Additionally, SWD is associated with an avoidance of social interactions and a general impairment in social functioning, increases the risk of alcohol addiction, use of psychoactive substances, and vehicular accidents. Accidents are the most common during the early morning, when the night shift workers return home and the early morning shift workers travel to work.

Therapeutic strategies recommended in SWD treatment include planning the time of major sleep episodes and naps, exposure to bright light, melatonin administration, and the use of hypnotics and psychostimulants [3]. If a patient must work a night shift, a short nap before going to work is beneficial. It significantly improves physical and mental performance, reduces the risk of accidents at work, and does not lead to a deterioration of sleep after the work shift ends. During the first half of a night shift, it is recommended for a patient to stay in a brightly lit room. However, intense light has to be avoided in the last hours of the night shift and when a patient returns home from work. When returning home after sunrise, the patient should wear dark sunglasses. In order to improve the quality of sleep after a night shift, a low dose, 0.5–3 mg, of melatonin can be used. The sleep period after a night shift should be not too long, it is advisable to use an alarm clock after 6–7 hours of sleep and to take a nap (up to 30 minutes) before going to work the next night. In the event of an early morning shift, the patient needs to schedule bedtime during the early evening hours (e.g., usually before 10 p.m., for a typical 8-hour shift at work: 10 p.m. to 6 a.m., 6 a.m. to 2 p.m., and 2 p.m. to 10 p.m.). Higher melatonin doses, 3–5 mg, should be administered 3 hours before the scheduled bedtime. During this time, bright light and stimulating activities should be avoided.

Despite their proven effectiveness, hypnotics should be used with caution and only temporarily in order to reduce the risk of dependence. Substances and stimulants (caffeine and modafinil) should only be used when, for reasons of safety, improvement of the wakefulness quality is required. The implementation of this form of treatment must, however, include an analysis of the negative effect of stimulants on the quality of sleep, both nocturnal and during the day following a night shift (modafinil and caffeine may lead to poor sleep quality over a 12-hour period after the initial intake).

The organization and scheduling of working hours by the employer can play an important role in the prevention and treatment of SWD. These should include planning for a fixed schedule of changes. Clockwise rotation of shifts is recommended, wherein an employee from an earlier shift moves to a later one. Schedules with quick shift changes should be used, i.e., a night shift should not be planned for more than two consecutive days, however, when it is not possible, the schedules with slow changes to the next shift should be used. The given shift should then last at least five consecutive working days and before moving to the next shift, an employee should be able to take two days off from work. Additionally, long shift durations should be avoided (e.g., 8-hours is recommended and should not exceed 12 hours). Finally, individuals who work in shifts should receive at least a 3-week vacation once a year.

Disorder associated with time zone changes (jet lag disorder)

The occurrence of sleep disorders and other physiological effects (e.g., from the digestive system) is a natural consequence of travel with the change of many time zones and is termed a jet lag syndrome. To diagnose jet lag disorder, symptoms of the syndrome have to be present for at least a few days after the journey and significantly affect the mood and daytime functioning.

For the diagnosis of jet lag disorder, the three following criteria must be met: [5]:

- A. There is a complaint of insomnia or excessive daytime sleepiness accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones.
- B. There is associated impairment of daytime functioning, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance) within one or two days after travel.
- C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Jet lag disorder is caused by a temporary misalignment of timing of the sleep-wake cycle generated by the endogenous circadian clock and the sleep-wake times required to adjust to the new time zone. The severity and duration of symptoms depends on the number of crossed time zones and the direction of travel. An eastward travel (i.e.,

phase advance in circadian rhythms and sleep-wake hours) is usually more difficult to adjust to than westward travel.

Diagnosis of jet lag disorder is based on the patient’s history and a physical examination. A careful assessment is required in order to determine whether reported symptoms do not result from another disease, e.g., mental disorders, somatic diseases, insomnia, exacerbated by the travel or the sleep deprivation caused before and during the trip. The Columbia Jet Lag Scale and the Charite Jet Lag Scale can be used for the assessment of jet lag symptoms and severity [10, 11]. Sleep logs and actigraphy monitoring are not required to evaluate the sleep-wake rhythm in jet lag disorder, and there is no need to assess other circadian biomarkers.

The following therapeutic strategies are recommended for jet lag-related prevention and treatment: gradual bedtime adaptation (before the flight) to the time at the destination, melatonin administration, light therapy, and behavioral interventions – meal and activity schedules [3]. Bedtime adaptation to the new time zone is particularly recommended when traveling eastward. Melatonin administration at the dose of 3–5 mg three hours before the bedtime for at least three days preceding the trip and one hour before bedtime at the destination is suggested. Furthermore, light therapy in the morning (light intensity 3,000 lux or more) is recommended as an aid to advance the sleep phase. Such a treatment should be initiated 3 days before travel and continued for 5 days after reaching the destination, and at the destination melatonin should be administered one hour before bedtime. When traveling westward, exposure to bright light in the evening is recommended, starting at 7 p.m. Administration of a low dose of melatonin, 0.5–1 mg, in the second half of the night can also be helpful, if the patient is woken up.

Travel with the crossing of 8 or more time zones requires a specific use of light therapy. It is possible that, before the adaptation to the local time at the destination, the endogenous clock will interpret dusk as dawn and vice-versa. In this case, an application of evening bright light can, paradoxically, evoke an advance and not a delay of the sleep phase (the body does not recognize light as an evening, but as a morning one). Therefore, in such travels, it is recommended to avoid light exposure at dusk and dawn for the first two days, and the bright light therapy should not be used before the third day at a new destination (Table 4).

Table 4. Recommendations to minimize the negative effects of jet lag disorder

Recommendations	Westward travel	Eastward travel
Before journey		
Begin adaptation to the new time zone	Delay bedtime, about 1–2 hours for a few days before the trip, in the evening, practice light exposure (stay in lightened rooms, use a computer, screen devices, and watch television)	Wake up earlier, about 0.5–1 hour for a few days before the trip, after awakening, practice the light exposure (stay in the lightened rooms, or go outside)

table continued on the next page

Use melatonin	Not recommended	Start melatonin treatment 3–5 mg at least 3 days before the journey, at least 3 hours before bedtime, avoid light after melatonin intake
Avoid sleep deprivation	Start the trip preparations in advance to avoid the need to stay up late before the departure, which can cause sleep deprivation	
During travel		
Avoid sleep deprivation	If possible, choose business class, which allows for more comfortable sleep, and use an eye mask along with the earplugs/headphones. The use of short-acting hypnotics (zaleplon 5 mg, zolpidem 5 mg) can be considered if you have a good tolerance of hypnotics and the time before landing is longer than 8 hours (there have been reported rare cases of hypnotics-induced complex behavioral disorders)	
Choose beverages carefully	Drink a lot of water to prevent dehydration, do not drink caffeinated beverages and, if you plan to sleep, do not drink alcohol	
Use antithrombotic prevention	Avoid wearing clothes that cause compression around the lower limbs and waist; stay hydrated and exercise your calf muscles whilst sitting in your seat to prevent local venous stasis. In the case of an increased risk of venous thrombosis, use compression stockings. Application of antithrombotic low-molecular weight heparin in the preventive dosage should be taken into consideration as well	
After landing		
Be aware of the possible difficulties	Troubles with physical and mental performance in the evening, difficulties maintaining sleep in the morning	Difficulties in falling asleep, waking up in the morning, as well as difficulties with physical and mental performance before noon
Use naps	If the travel evoked sleep deprivation, take a short nap, no longer than 30 minutes, so that it will not influence nocturnal sleep	
Use melatonin	Use a low dose of melatonin, 0.5–1 mg, in the second half of the night in the case of very early morning awaking	Use melatonin in a dose of 3–5 mg one hour before the bedtime of the new time zone
Use light exposure	Stay in a bright, lightened room in the evening	Stay in bright, lightened rooms or go out in the morning
Travels crossing more than 8 time zones	Avoid an exposure to intensive light in the evening for the first two days in a new place, as well as initiate bright light exposure in the evening starting from the third day at a new destination	Avoid an exposure to intensive light in the morning for the first two days in a new place, and initiate bright light exposure starting from the third day at a new destination
Drink caffeinated beverages carefully	Caffeine improves wakefulness during the day, however, when used in the afternoon it has a negative effect on nocturnal sleep quality	

Sleep-wake rhythm disorders in children

Among the seven circadian rhythm disorders described in the ICSD-3, DSWPD is the most commonly observed in children and adolescents. It is estimated that approximately 7% to 16% of adolescents suffer from this disorder [12]. Those who are most susceptible are older children and adolescents who report recurring difficulties initiating sleep. Sleep onset usually occurs a few hours (more than two) later than socially accepted sleep times (usually between 1 a.m. and 6 a.m.). It results in difficulty waking up in the morning and excessive daytime sleepiness [13]. With puberty, there is a tendency to develop a delayed sleep pattern which results in sleep deprivation. Adolescents' total sleep time is often around 7 hours, instead of the recommended 9 hours, which leads to chronic sleep deprivation [14]. In addition to physiological factors, psychosocial conditioning plays a significant role in the development of DSWPD. Changes in social life patterns, i.e., using social media late in the evening, are often associated with the use of light emitting electronic devices, especially in the evening and at night.

Reduced parental control, a tendency to complete homework in the evening, and consuming products with caffeine and other stimulants are also significant factors that delay the sleep phase in this age group [13–15]. It is also important to mention that approximately 40% of adolescents with DSWPD have a family history of the disorder. Neglecting sleep hygiene, taking naps during the day, delaying bedtime for at least 2 hours on days off from school and weekends, together with waking up 3–4 hours later in the morning than typically observed on the school days, significantly impedes the normal regulation of the sleep-wake rhythm in adolescents [13, 14].

The negative effects of DSWPD in this population may be observed as school failure related to being repeatedly late for school and/or repeated absences. The need to adapt to school hours causes chronic sleep deprivation [14], introducing troubles in the regulation of the circadian rhythm. Other consequences of DSWPD in adolescents are difficulties in social interactions or mood complaints. It is estimated that more than half of young DSWPD patients experience mood disorders, increasing the risk of the use of psychoactive substances and suicidal thoughts [13].

In younger children, the delayed sleep phase may cause pre-sleep alertness during the hours the child is expected to go to bed, which in turn causes oppositional behaviors and bedtime resistance. It is believed that the prevalence of DSWPD is higher in children and adolescents with attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and anxiety disorders, which may aggravate the symptoms of the primary disorder [16, 17].

DSWPD diagnosis in children and adolescents should be based on the standard diagnostic criteria, preceded by the analysis of a 14-day sleep diary (a minimum of 7 days), and whenever possible actigraphy monitoring during both school days and weekends.

The recommendation for DSWPD treatment in children and adolescents is a strict adherence to sleep hygiene together with planning a regular waking up time (and bedtime) during both school days and weekends. The use of light emitting electronic devices should be limited, at least for one hour before going to bed. Gradual advancements of the time of morning wake up time is also recommended, e.g., 15–30 minutes earlier per week. Regulation of the biological clock can be further enhanced by bright light therapy in the morning (30 minutes to 2 hours, depending on the light intensity), the effectiveness of which, in combination with behavioral interventions, has been proven in research studies [2]. Recent meta-analyses have shown that melatonin is also effective and can be safely used in the treatment of DSWPD in children and adolescents without comorbidities [18, 19] as well as in comorbid psychiatric disorders, such as ADHD [20] or ASD [21]. The recommended dose of melatonin in children and adolescents is 1 to 10 mg/day, administered in a close relation to DLMO [16]. The melatonin doses in children populations are often higher than those recommended for adults.

N24SWD occurs when the endogenous circadian sleep-wake rhythm is, in most patients, longer than 24 hours. The common underlying mechanism consists of a failure to synchronize with environmental time cues. Therefore, a patient's sleep onset and offset are constantly delayed which causes alternating periods of daytime sleepiness, insomnia and short periods during which the patient's sleep-wake rhythm is in accordance with the expected one. This disorder mostly affects blind children and adolescents, who are unable to perceive light, which is the main time cue. N24SWD can also develop in teenagers who are immobilized or have few social contacts due to medical condition. There are also reports that both untreated DSWPD and DSWPD treated with planned shifts in sleep period timing may transform into N24SWD [22].

The recommendation for the treatment of N24SWD is strict adherence to sleep hygiene and controlling the intensity of external stimuli depending on the time of the day. Exposure to bright light in the morning (except for blind patients) and using a 3–10 mg dose of melatonin (an hour or two before the scheduled bedtime), which is particularly effective in blind patients, is also recommended. After 6 to 12 weeks of the treatment, a reduction of melatonin dose to 1–3 mg/day is advised.

ISWRD is characterized by a lack of a clearly defined circadian sleep-wake rhythm and is extremely rare in healthy children. Total sleep time does not usually differ from the appropriate for child's age, but there are several (at least three) sleep episodes during the day and randomly occurring periods of sleep and wakefulness at different times of the day [12]. ISWRD is most commonly observed in adolescents with intellectual disabilities and neurodevelopmental disorders [12, 14]. The prevalence of sleep disorders in this group of pediatric patients is estimated to be 13% to 86% [16]. ISWRD diagnosis in children and adolescents should be based on the standard diagnostic criteria and the analysis of a 14-day sleep diary (minimum of 7 days), and, whenever possible, actigraphy monitoring during both school days and weekends.

In children with ASD, there is a reduction in the amplitude of the diurnal melatonin level (with a smaller melatonin peak at night) and the cortisol level higher than that typically observed in the general population [23]. Irregular sleep episodes in children with neurodevelopmental disorders require the constant presence of parents and caregivers, which consequently leads to chronic sleep deprivation, with its consequences, among these individuals [14].

Recommendations for the treatment of ISWRD involves a compliance with behavioral interventions aimed at maintaining the patient's activity during the day, together with the reduction and control of stimuli during the sleep period [12]. Adherence to sleep hygiene, collectively with planning regular bedtime and waking up time, and avoiding naps is also important. The use of melatonin in the evening (as in the case of N24SWPD) combined with behavioral interventions is reported to be effective in the treatment of ISWRD in children with intellectual disability and neurodevelopmental disorders. As a result children exhibit sleep consolidation and reduced daytime sleepiness, which helps to avoid naps and eventually improves the regularity of the sleep-wake rhythm [24–27]. Studies confirm the efficacy of melatonin use in children with autism spectrum disorders [21], Angelman syndrome [28], tuberous sclerosis [29], and Rett syndrome [26]. The efficacy of light therapy in ISWRD is found to be limited [14].

Recapitulation

A large group of patients that complain about insomnia or excessive sleepiness during the day, in fact suffer from CRSWD, which is associated with the malfunctioning of the biological clock and a lack of biological and/or social synchronizers. Hypnotics and stimulating substances, most frequently used in the treatment of insomnia or hypersomnia, have a limited efficacy in CRSWD. When administered at the usually recommended time they do not match the patient's own biological rhythm.

The standard treatment of CRSWD are chronobiological interventions, which improve the functioning of the biological clock and regulate the circadian sleep-wake rhythm. The main problem in this group of patients results from the wrong diagnosis. In clinical practice, it is frequently observed that patients with endogenous CRSWD are being treated for insomnia or excessive sleepiness for many years and often do not receive proper “chronobiological” treatment.

Therefore, it is necessary to include the elementary questions in the diagnostic process, which allows a physician to differentiate CRSWD from other sleep disorders.

A patient should be asked the following questions:

- 1) What is the typical sleep pattern on weekends, holidays, and days off work?
- 2) Does he/she work in shifts, have irregular or unconventional working hours, e.g., early work shifts?
- 3) Does he/she often travel with crossing of time zones?

Once the circadian rhythm disorders are diagnosed, another key issue is to establish whether these changes in rhythms are “genetic” or “learned”:

- 1) What is the typical sleep pattern in other family members?
- 2) What was the typical sleep-wake rhythm like in childhood?

In addition to the effective chronobiological interventions (melatonin, light therapy), the treatment of CRSWD also includes educating the patient and simple behavioral interventions, which regulate times of sleep and wakefulness in order to adjust them to the rhythm of a 24-hour day.

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