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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 I. Physiology, assessment and therapeutic methods

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Summary

Majority of the physiological processes in the human organism are rhythmic. The most common are the diurnal changes that repeat roughly every 24 hours, called circadian rhythms. Circadian rhythms disorders have negative influence on human functioning. The aim of this

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article is to present the current understanding of the circadian rhythms physiological role, with particular emphasis on the circadian rhythm sleep-wake disorders (CRSWD), principles of their diagnosis and chronobiological therapy. The guidelines are based on the review of recommendations from the scientific societies involved in sleep medicine and the clinical experiences of the authors. Researchers participating in the preparation of guidelines were invited by the Polish Sleep Research Society and the Section of Biological Psychiatry of the Polish Psychiatric Association, based on their significant contributions in circadian rhythm research and/or clinical experience in the treatment of such disorders. Finally, the guidelines were adjusted to the questions and comments given by the members of both Societies. CRSWD have a significant negative impact on human health and functioning. Standard methods used to assess CRSWD are sleep diaries and sleep logs, while the actigraphy, when available, should be also used. The most effective methods of CRSWD treatment are melatonin administration and light therapy. Behavioral interventions are also recommended. A fourteen-day period of sleep-wake rhythm assessment in CRSWD enables accurate diagnosis, adequate selection of chronobiological interventions, and planning adequate diurnal timing of their application. This type of assessment is quite easy, low-cost, and provides valuable indications how to adjust the therapeutic approach to the circadian phase of the particular patient.

Key words: circadian rhythm, assessment, physiology

Introduction

In a two-factor model of sleep regulation, apart from the homeostatic process, circadian rhythm is the primary mechanism influencing the length, quality, and time of sleep [1, 2]. Typically, the desynchronization of circadian rhythms can be caused by the widespread exposure to artificial light in the evening and/or at night, along with a low exposure to sunlight during the day. The lack of physical activity, many hours of mental activity during the day (especially in the period immediately before going to sleep), irregular mealtimes, shift work and/or an irregular work schedule, can also contribute to the Circadian Rhythm Sleep-Wake Disorders (CRSWD). CRSWD resulting in poor quality of sleep and deterioration of the psychophysical efficiency during the day are found to be a common public health concern in the developed countries. However, the knowledge of physicians and public awareness of the physiological importance of circadian rhythms and methods of CRSWD treatment are insufficient. Frequently, these sleep disorders are treated in the same way as insomnia with the use of hypnotics, which have a low efficacy in the treatment of CRSWD.

Aim

The aim of this article is to provide recommendations concerning the principles of CRSWD diagnosis and treatment, elaborated by Polish experts. The first part of the guidelines presents the current state of knowledge of the circadian rhythm physiology, the principles of its assessment, and the use of chronobiological therapeutic methods. In the second part, the principles of CRSWD diagnosis and treatment are described [3].

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 consist of proposed Polish standards for CRSWD treatment based on the analysis of recommendations published by other scientific societies [4–6], the Third Edition of the International Classification of Sleep Disorders [7], and the authors' opinions. Experts participating in the panel were invited by the Boards of the Society and the Section, based on their significant contributions in circadian rhythm research and/or many years of clinical experience in the treatment of such disorders. In addition, the final version of the guidelines took substantial consideration to the questions raised from participants of the above-mentioned convention and comments based on the initial guideline proposal by the members of the Society and the Section.

Circadian rhythms: physiology and importance for well-being

Living organisms, including humans, require the adjustment of physiological processes and behavior to the conditions of a 24-hour day-night period, as a consequence of the Earth's rotation around its axis. The inevitable sequence of light and darkness was a driving force for the evolution of adaptive mechanisms that allow organisms to anticipate these changes and to prepare adequately to behavioral and metabolic challenges. It is obvious that the opposite physiological processes, such as movement and rest or sleep and wakefulness, cannot take place simultaneously or be conducted with the same intensity. This justifies the need for an endogenous mechanism that generates and synchronizes the course of physiological processes in humans. This mechanism is referred to as a biological clock, which governs the circadian rhythms (and seasonal cycles) [8–11]. Biological rhythms are defined as the diurnal changes in the intensity of physiological processes, with the maximal and minimal values occurring in the successive days with the same regularity. In the absence of external time cues (also called "Zeitgebers", the German word for "time givers"), these rhythms do not last exactly 24-hours. Therefore they are called circadian rhythms. The source of these regular changes is a biological clock which is located in the hypothalamic part of the central nervous system, in the suprachiasmatic nuclei (SCN) [9]. Progress in molecular biology allowed for the understanding of basic mechanisms of the biological clock, which proved to be universal. There is an universal molecular mechanism present in all living organisms, only the way of practical organization is different [12]. This mechanism, however, is always based on rhythmical turning transcription of specific types of genes, so-called clock genes, on and off, resulting in appropriate intensity of the controlled processes during day and night [13]. Synchronization of the endogenous clock with environmental conditions allows for the rhythmical changes in the majority of physiological processes and behavior to be in concert with the external world. The synchronizing factors are clear environmental cues (so-called time givers), of

which the most important for the clock in the SCN is light, more precisely, alternating periods of light and darkness, i.e., day and night. Such cues impose the period of activity and rest (sleep). Thus, humans and many non-human diurnal species experience nighttime sleep and daytime wakefulness. In contrast, nocturnal species sleep during the day and perform physical and other activities at night [8].

The master (central) clock is located in the mammalian SCN, however it is not the sole clock mechanism involved in the temporal organization of physiological processes. Namely, majority of organs and tissues are equipped with similar molecular mechanisms, called the peripheral clocks. The most well-known among them are clocks located in the liver, adipose tissue, and gastrointestinal tract. The time givers for the peripheral clocks comprise mainly of meals: their timing, quantity and composition. Neurohormonal signals generated in the peripheral organs control not only their function but also reciprocally modify the diurnal activity of the master clock [14]. Therefore, every environmental event that disrupts the peripheral clock function can also affect the SCN master clock [10]. The homeostasis of the body is ensured by a complex clock system, the functioning of which largely depends on life conditions, therefore factors that desynchronize the endogenous clock, e.g., light at night, changes in bedtime or mealtimes, or changes in times of meals and sleep associated with night-shift work, or transcontinental traveling can have an adverse effect on the functioning of the body. This in turn can lead to insomnia, depression, and metabolic disorders (obesity, diabetes type 2), which are classified as so-called civilization-related diseases [15].

Human physiological processes exhibiting a circadian rhythmicity include, but are not limited to, sleep and wakefulness, body temperature, metabolism and energetic homeostasis, heart rate, peripheral vessels resistance and blood pressure, blood viscosity and plasma fibrinolytic activity, synthesis and release of proinflammatory cytokines and hormones (cortisol, melatonin, prolactin, growth hormone), secretion of gastric juices unrelated with food, as well as lung volumes and ventilatory flows. Circadian rhythms change throughout the human lifespan. In newborns, the sleep and activity rhythms are strictly ultradian. It means that they have a period of several hours. In the elderly, two basic parameters of the circadian rhythmicity are changed: amplitude of circadian rhythms of particular physiological process is reduced and the period of circadian rhythms is shortened. In some pathological circumstances, the circadian rhythmicity in the elderly is lost. For example, in individuals suffering from Alzheimer's disease there is a progressive decrease in the activity and number of SCN neurons which can disrupt the ability of the SCN to coordinate other circadian clocks [11].

Rhythmic variations in the intensity of human physiological processes are related with the diurnal rhythms of the onset and intensity of symptoms of numerous diseases, including rheumatoid arthritis, asthma, coronary heart disease, cardiac arrhythmias, hemorrhagic and ischemic stroke, epilepsy, headaches, gastric and duodenal ulcers, gastroesophageal reflux, and biliary colic [16]. It should be emphasized that the therapeutic effectiveness and toxicity of many oncostatic drugs can vary rhythmically over 24-hours [17].

Methods of circadian rhythm assessment – sleep diaries, sleep logs, and clinical scales

Standard methods used to assess sleep disorders related to perturbed circadian rhythmicity are sleep diaries while chronotype scales (morningness–eveningness) can be used optionally [5]. Prior to the assessment of circadian rhythms, it has to be verified whether a patient has recently travelled with crossing time zones or whether working hours have been extended behind the hours between 8 a.m. and 8 p.m. The patient should also be asked about the amount of time exposed to light, the times of meals, as well as duration of mental and physical activity within a day. The obtained information should take into consideration the age and sex of the patient.

Sleep diaries are self-report measures, usually completed by a patient at home. It allows an evaluation of the sleep-wake rhythms in the patient's natural conditions. The minimum duration of reporting in a sleep diary is 7 days. However, it is recommended to extend the recording to 14 days as it provides a more accurate and reliable evaluation of the sleep-wake rhythm. In the circadian rhythms analysis it is also important to document the times of sleep in the periods free from school or work. The optimal period of the sleep-wake rhythm recording is a time during vacation/holidays, and when impossible, the reporting should include at least two weekends. There is a standard sleep diary proposed by the American Academy of Sleep Medicine, which is also available in Polish [18, 19]. For patients with CRSWD, the Polish group of experts recommends using a chronobiologic sleep diary, which focuses more on the time of beginning and ending of the sleep period, and makes a distinction between the records obtained during the working days and the days off (Figure 1).

Figure 1. **Chronobiologic sleep diary recommended by the Polish experts to diagnose and during the treatment of CRSWD**

First and last name: time of going to sleep:

No. of week of the therapy: time of waking up:

Please fill each day after waking up.

Please use the 24-hour time format.

1	Today's date							
2	Is today your day off?							
3	What time did you get into bed?							
4	What time did you try to fall asleep?							
5	How long did it take you to fall asleep?							

table continued on the next page

6 What time was your final awakening?							
7 Did you use an alarm clock?							
8 What time did you get out of bed?							
9 How do you rate the quality of your sleep?	□ very poor □ poor □ fair □ good □ very good	□ very poor □ poor □ fair □ good □ very good	□ very poor □ poor □ fair □ good □ very good	□ very poor □ poor □ fair □ good □ very good	□ very poor □ poor □ fair □ good □ very good	□ very poor □ poor □ fair □ good □ very good	□ very poor □ poor □ fair □ good □ very good
10 Comments (optional)							

Instructions for completing the chronobiologic sleep diary:

- Sleep diary should be completed every day, preferably within one hour after getting out of bed, when the recall of sleep pattern is more accurate.
- Use a 24-hour time format. For example, 22:30 instead of 10:30 p.m., to reduce the risk of error.
- The log may be used by people with atypical hours of sleep – in this case, questions should refer to the longest episode of sleep.

Instructions for each question:

1. Today's date: enter the date of completion of the sleep diary, i.e., the date of the morning.
2. Is today your day off?: Please Enter "Y", if the current day is a non-working day or weekend/holiday, or "N" if it is a working day. This refers to the day following the getting out of bed corresponding to the date indicated in question 1.
3. What time did you get into bed? Indicate the time of physically getting into bed. It is important to note that getting into bed may not be the same time as falling asleep. For instance, some people might lie in their bed prior to attempting to fall asleep, e.g., read a book or watch TV, while others immediately try to fall asleep.
4. What time did you try to fall asleep? Indicate the time you decided to attempt to fall asleep. For example, some people might try to fall asleep once they get into bed.
5. How long did it take you to fall asleep? Indicate the estimated time (in minutes) that you think passed from the moment you went to sleep (Question 4) until actually falling asleep.
6. What time was your final awakening? Indicate the time of your last awakening, after which you no longer slept.

7. Did you use an alarm clock? If an alarm clock was used, meaning that the awakening occurred as a direct result of an alarm sound or through other assistance aimed at awakening (e.g., wake-up calls, wake-up by roommate etc.). On the other hand, if you woke-up before the alarm sound, and you did not use its help, enter "N".
8. What time did you get out of bed? Indicate the time of getting out of bed which may be the same or later than the time of final awakening. For instance, some people after their final awakening do certain activities before getting up (e.g., read a book, check e-mail).
9. How would you rate the quality of your sleep? Indicate your subjective evaluation of whether the sleep was good or not.
10. Comment (optional): Please write whether your sleep was disturbed by some unusual event (e.g., illness, an unusual noise from the outside, noisy neighbors). You should make a short comment that briefly describes an event(s) disturbing your sleep during this particular night.

The most accurate assessment of the circadian rhythm is to analyze the period of sleep not limited by the scheduled awakening, e.g., on the days off from work or school. A sleep diary should be completed once a day, every morning, within an hour after the last awakening in order to reduce the risk of forgetting sleep patterns.

Chronotype rating scales are self-report measures completed by a patient. Although they do not provide such a precise description of the circadian functioning as sleep logs do, they can be used for a rapid (within 10 minutes) initial assessment of the circadian rhythm (e.g., when a patient awaits for medical advice). It is recommended to use the Composite Scale of Morningness (CSM) [20], an improved version of the well-known Morningness-Eveningness Questionnaire (MEQ) by Horn and Östberg [21]. Both scales are available in the Polish language version [19, 22]. The CSM consists of 13 single choice questions. A higher overall score indicates greater morningness, while a lower score indicates greater eveningness. The completion of the CSM takes approximately 5 minutes. For a more precise description of circadian rhythms, results of the CSM may be analyzed in the subscales of the Morning Affect (questions 3–6, 11, 12) and the Circadian Preferences (questions 1, 2, 7–10, 13) [19, 22]. Assessment of the circadian rhythm can also be based on the Munich Chronotype Questionnaire (MCTQ) [23], containing questions akin to those present in sleep diaries, except that questions refer to a typical week and not solely to the previous day. The MCTQ has been used in the Polish study [19] and is available in the Polish language.

CRSWD should be suspected when following parameters of sleep pattern are documented based on sleep diary and chronotype rating scales:

In the delayed sleep-wake phase disorder (DSWPD):

1) the weekend wake times are much later compared to the working days;
2) the total sleep time on weekdays is shortened to less than 7 hours and longer than 8 hours on days off from work;

3) sleep latency on working days is more than 30 minutes or longer, if an individual's bedtime is earlier than on holidays/days off. If an individual goes to bed late, sleep latency is within the normal range (i.e., less than 15-30 minutes, for the people before and after the age of 30, respectively);
4) the overall score of the CSM and its both subscales remains low.

In the advanced sleep-wake phase disorder (ASWPD):

1) wake times are earlier compared to the typical values in the age-matched group;
2) a characteristic feature is waking up at an early hour repetitively, also when the bedtime is later than usual;
3) the CSM scores are high.

In the irregular sleep-wake rhythm disorder (ISWRD), keeping a sleep diary often requires the support of a caregiver, since the patients frequently are children with complex neurodevelopmental disorders or elderly persons with neurodegenerative diseases. A characteristic feature is the presence of several sleep episodes over 24 hours (a minimum 3), instead of one main sleep period. In such cases, instead of the standard sleep diary, a graphical sleep log is used, in which a patient marks the

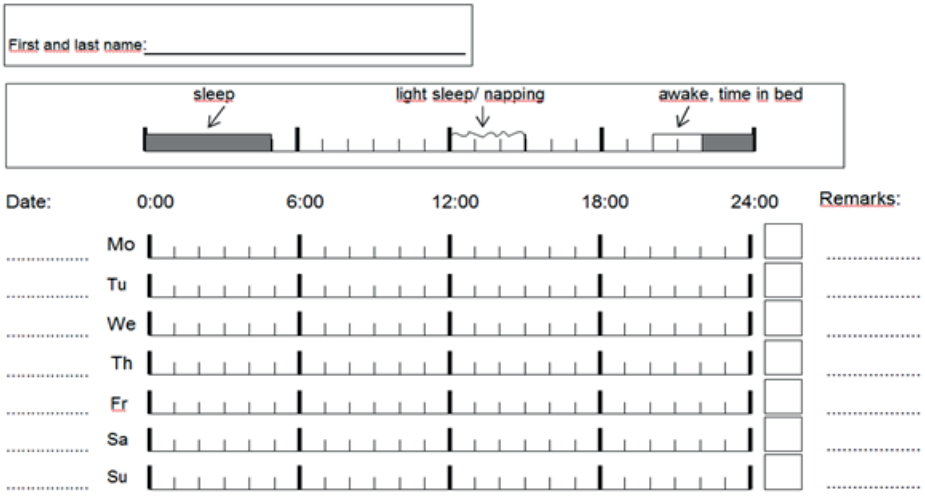

Figure 2. **Graphical sleep log (adapted, after permission, from the sleep log used at the Sleep Disorders Center in the Department of Psychiatry, University in Regensburg, Germany)**

Instructions: the sleep log has to be completed after each sleep episode. In addition, it should also contain a record of naps and the inability to sleep. Patient can also indicate the time of other activities, e.g., a star denotes the time of taking medications. The square window "Remarks" on the right side is a space for the patient to enter a subjective assessment of their sleep quality, at a scale fixed with a doctor, e.g., 1–6. This window may also be used for the patient's subjective assessment of other important parameters, e.g., mood or severity of sleepiness.

periods while he/she slept, when he/she could not sleep, and when he/she was taking a nap (Figure 2). The recommended period of reporting in the graphical sleep diary is at least 14 days.

In a non-24-hour sleep-wake disorder (N24SWD), keeping a sleep log requires another person's help as well, because most of those patients are blind. In a sleep log, a successive shift in the time of the main sleep episode (a free-running rhythm) towards the later hours is observed (in the rare cases it shifts towards the earlier hours).

Methods of the circadian rhythm assessment – biological markers

The standard biological method for assessing the circadian rhythm is to assess the rhythm of rest and activity, i.e. actigraphy. The measurement is performed with a small watch-like device that is equipped with motion and light sensors, and is usually placed on the wrist of the non-dominant hand. In general, the actigraphy and sleep diaries/logs are collectively used in the diagnosis of CRSWD because it allows to measure sleep in an objective and subjective manner. The actigraphy is used to register several parameters of sleep – amount of time in bed, sleep latency, total sleep time, sleep efficiency (ratio of the time spent asleep to the time spent in bed, expressed as a percentage), amount of time awake after sleep onset, and the time of the final morning awakening. It also records naps and physical activity during the day. Actigraphs that contain light sensors allow for the measurement of time and intensity of light exposure. In addition, amplitude, stability, and variability of circadian rhythms can also be assessed [24].

Moreover, circadian rhythms can be objectively evaluated by the measurement of the clock-controlled physiological processes. Such measurements include the onset of melatonin secretion in the dark (dim light melatonin onset – DLMO), daily changes in the concentration of 6-sulphatoxymelatonin (aMT6s) in the urine, and the circadian rhythm of a core body temperature. Among these measures, evaluation of DLMO is the most commonly used. During this assessment, a patient has to remain under very low light intensity (not exceeding 10 lux) for the whole test duration [25]. The test is usually carried out in a laboratory equipped with a toilet, with the low light intensity in all rooms, and the hours of measurement have to be adjusted to the clinical indications and a patient's age. In practice, for the majority of patients, it is sufficient to collect a sample of saliva every hour and to start the test 6 hours before the usual bedtime, based on the data from a sleep diary/log. The first sample of saliva is collected after a patient has stayed in a dark room for one hour, consecutively at each hour, with the last sample around the usual bedtime. Apart from the compliance with a regime of the low light intensity, the examinee cannot eat or drink for 30 minutes before each saliva sample collection, and after eating he/she should rinse his/her mouth with water. During the measurement, physical activity should be also avoided. In a recently published study [26], it was demonstrated that DLMO can be also assessed at the patient's home, with a small decrease in the reliability with

appropriate test regime. This provides promise for the future dissemination of this biological marker in the CRSWD diagnosis. In clinical practice, the evaluation of the circadian rhythm of aMT6s concentration in urine and core body temperature is more difficult to implement than the evaluation of DLMO. Measurement of aMT6s involves the collection of a urine sample every 2–8 hours (a patient waking-up from sleep is avoided) for a period of 24–48 hours [27]. The recommended period of the core body temperature rhythm registration is 36–40 hours in the sleep laboratory with constant conditions [28]. The standard registration is performed using a rectal probe and is not willingly performed by the patients because of inconvenience and discomfort. However, the recent introduction of special disposable capsules that are fitted with temperature microsensors can replace the utilization of a rectal probe. Such capsules can be swallowed by the patient and excreted in the feces. Although the measurement of biological markers is not commonly performed in clinical practice, it is an essential tool in scientific research to examine circadian rhythms and precisely describe their parameters (Table 1).

Table 1. **Characteristic parameters of circadian rhythm**

Parameter	Evaluation method
Duration of the active phase (α)	Recorded by the actigraphy or calculated according to the sleep diary.
Duration of the resting phase (ρ)	Recorded by the actigraphy or calculated according to the sleep diary.
Chronotype (ψ)	Time of the mid-sleep occurrence evaluated based on the MCTQ, sleep diary or actigraphy; compared with the scores of the CSM or the MEQ
Internal synchronization	Time shift between the mid-sleep and DLMO. Evaluated on the basis of DLMO test combined with the data provided in the sleep diary.
External synchronization	Time shift between the mid-sleep or DLMO and the beginning of darkness.
Period (τ)	The period of the endogenous rhythm manifested in the subsequent days of measurement in isolation from the external environment and time indicators, in case of sleep rhythm usually slightly longer than 24 hours.
Rhythm mesor, acrophase and nadir	Mesor – diurnal average value of the tested parameter; acrophase – time of day with the highest value (maximum) of the examined parameter; nadir – lowest value (minimum) of the examined parameter.
Rhythm amplitude	Difference between the minimal (or maximal) value and the diurnal average value (mesor) for the rhythms similar to the sine wave, and for other rhythms – difference between maximum and minimum.
Rhythm stability/variability	Changes in time of DLMO in the subsequent days or weeks, or stability of activity/rest rhythm in actigraphy for at least 7 days.
Drift	Rhythm phase shift in time (direction and magnitude) in the subsequent days.

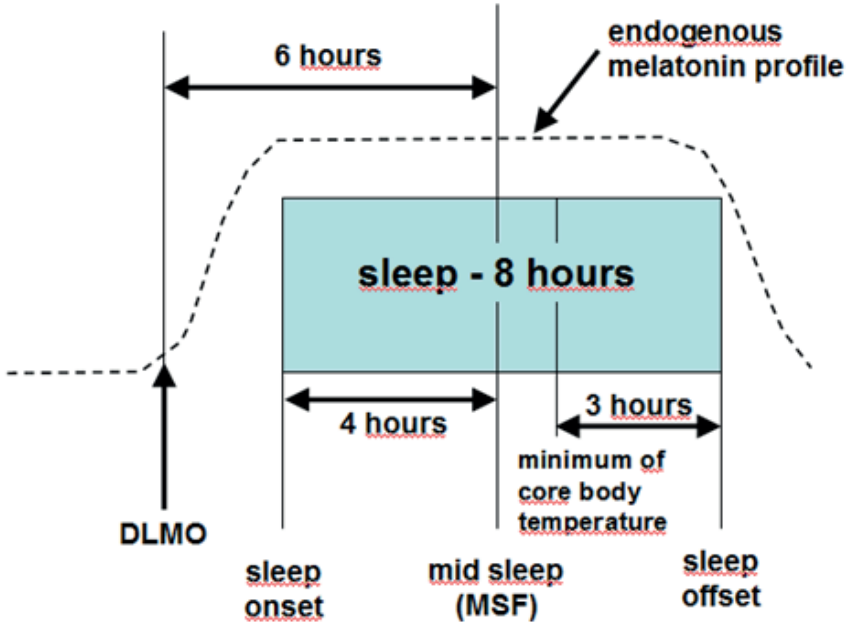

Figure 3. **Graphical presentation of the timing of DLMO and a minimum core body temperature based on the data from a sleep diary (adapted with permission from [30]. Copyright by National Academy of Sciences in 2006, non-commercial, educational use under the terms for obtaining consent)**

DLMO – dim light melatonin onset; MSF – mid-sleep on free days

Treatment of circadian rhythm disorders

Standard methods of CRSWD treatment are melatonin administration, light therapy, and avoiding light exposure at the time of day scheduled by a physician. These methods of treatment are the most efficient because light is a major factor synchronizing the circadian rhythm. Behavioral interventions which affect the light-independent circadian regulation are also used in the treatment of CRSWD. These interventions include planning of times for meals, physical, social, and mental activity, along with the timing of sleep and naps. Although the recommendations for the use of additional behavioral interventions in the treatment of CRSWD are not based on properly conducted clinical trials [4], they are usually included in the treatment schedule. In our opinion, the lack of compliance with the rules of behavioral interventions substantially decreases the well-known effects of melatonin and light treatment on circadian rhythms. Some techniques of cognitive-behavioral therapy used in the treatment of insomnia, like sleep restriction therapy, stimulus control, cognitive restructuring, relaxation techniques and sleep hygiene, may be also useful in the treatment of CRSWD. However, although

this method is currently the standard method for treatment of chronic insomnia [29], it is not an effective treatment of CRSWD, wherein chronotherapeutic interventions are needed.

Studies on biological markers implicated in circadian rhythms have established the optimal timing of melatonin and/or light therapy administration. These studies [25, 30] showed that the largest phase shift occurs when melatonin and light therapy are applied in concordance with DLMO occurrence and a core body temperature minimum. The relationship between the phase shift strength, time and type of intervention, is presented graphically as a phase response curve.

When the data concerning the biological markers of circadian rhythm are not available, the time of the middle point of sleep on free days (mid-sleep on free days – MSF) should be established on the basis of a sleep diary/log. Usually DLMO precedes MSF by about 6–7 hours, while the core body temperature minimum occurs after the MSF, about 3 hours before the time of awakening (Figure 3).

Additionally, if the patient gets out of bed irregularly, it is recommended to normalize this timing and to follow the same hours of getting up on the working and free days as well. The strongest phase advance occurs when melatonin is administered at least 10 hours before a usual time of getting up and light therapy is used during the last 2 hours of the usual sleep period. The strongest phase delay occurs when melatonin is administered in the last 2 hours of the usual sleep period and light therapy is used during the first half of a usual sleep period.

Melatonin – "hormone of darkness": the regulation of circadian rhythm disorders

In humans, as well as in other vertebrates, melatonin is produced mainly in the pineal gland, and immediately released into the cerebrospinal fluid and into the bloodstream. In target tissues, melatonin exerts its biological activity through specific receptors. Regardless of the diurnal pattern of physical activity: nocturnal, diurnal or mixed, pineal melatonin is produced in a circadian rhythm with the high levels at night (dark period) and low during the day; hence its name "hormone of darkness". In humans, under standard lighting conditions, the onset of melatonin secretion is usually between 9.00 and 10.00 p.m., and the maximum plasma concentration (in adults 60–70 pg/ml) is achieved between 2.00 and 4.00 a.m. The secretion of melatonin substantially decreases between 7.00 and 9.00 a.m. [31]. Seasonal changes in the length of night (i.e., darkness occurring in nature), impose the duration of increased biosynthesis of the pineal melatonin and its release into the blood. Therefore, melatonin blood concentration consists of a chemical message on the length of day and night for all tissues and organs [32]. Therefore, melatonin functions as a "calendar" for the wild-living animals adjusting their physiology to the season. Living in the conditions of unrestricted access to artificial light sources, humans are unable to "measure" the seasonal changes with the length of nocturnal melatonin synthesis in the pineal gland. Therefore, the seasonal role of melatonin in humans has not been clearly explained so

far, but it cannot be ruled out that melatonin may contribute to the incidence of several seasonal changes in human physiology (body weight, appetite, and sleepiness) and psychological functions (mood, activity, and drive).

In many vertebrates, melatonin plays an important role in the regulation of circadian rhythmicity. The time course of the melatonin circadian rhythm is controlled by the master clock located in the SCN is considered the most reliable indicator of this clock's functioning. Among all known biological rhythms, the melatonin rhythm is to a lesser extent modified by the factors such as physical activity, sleep, mealtimes, or stress. However, it may be affected by light conditions, ongoing inflammation and, to a lesser extent, by the position of the body. Melatonin is involved in the synchronization of circadian rhythms, including those of sleep propensity and the core body temperature [31]. In conditions of a very low nocturnal level of plasma melatonin, the amplitude of core body temperature rhythm is reduced and sleep quality is deteriorated. In normal conditions, sleep usually begins 1 to 2 hours after the onset of the nocturnal melatonin secretion and ends 1 to 2 hours before the melatonin secretion becomes the lowest. It has been also evidenced that in humans melatonin affects the circadian aspects of the circulatory system, the maintenance of glucose homeostasis, and the immune system function.

The circadian rhythm of melatonin synthesis in humans diminishes gradually with age, particularly after the age of 55. Moreover, a decrease in the amplitude of melatonin rhythm is observed in patients with Alzheimer's disease, in which not only the nocturnal hormone production is lower but also it is elevated during the day. In addition, progression of the disease exacerbates these changes. It is suggested that the disturbances in the circadian organization of certain vital functions (e.g., abnormal sleep-wake rhythm) in the elderly may be related to the weakening of the melatoninergic signal [33]. Inverted melatonin rhythms (high levels during the day and low at night), correlated with the impaired sleep-wake rhythm was found in the people with Smith-Magenis syndrome [34]. Perturbed melatonin synthesis and rhythm (amplitude, phase, cycle length) may result from certain drug usage (e.g., the synthesis of melatonin is inhibited by β-blockers and intensified by antidepressants from the group of selective serotonin reuptake inhibitors), light exposure at night (e.g., night-shift workers), conditions of constant light intensity (e.g., people on orbital/polar stations and cavers), and rapid time zone crossing (transcontinental flights) [31]. In blind people, who are unable to perceive light as a synchronizer of the master clock, there is a non-24-hour rhythm of changes in the melatonin synthesis and release into the bloodstream [35]. Since these disorders often involve irregularities in the course of the sleep-wake rhythm, therapies targeting the melatoninergic system are used in the chronobiological treatment of sleep disorders [4]. To be effective, these therapies have to be used at a specific time of day. The right time of application is particularly important in the treatment with immediate-release melatonin, which is administered orally and reaches the maximal blood concentration within 40 minutes with a half-life of 30 to 50 minutes [36]. In the treatment of the circadian rhythm disorders, melatonin administration is

often combined with light therapy, which switches off the biosynthesis of endogenous hormone at the appropriate time. Melatonin treatment is mainly addressed to patients aged over 55, blind people, and in CRSWD. In the treatment of insomnia, it is preferable to use a slow release melatonin, in the dose of 2 mg after a meal, 1 to 2 hours before bedtime [6]. In our opinion, in the treatment of circadian rhythm disorders an immediate-release melatonin is more efficient as it reaches the maximum plasma concentration at the desired time, evoking the circadian rhythms shift and/or synchronization. Only melatonin as prescription or over the counter drug should be used for the medical purposes. In experimental research, the range of melatonin doses used is quite wide and varies from 0.5 to 10 mg [4]. Supporters of low dose melatonin treatment indicate that after melatonin administration in the dose of 0.5 mg an increase in serum melatonin concentration is close to the maximal physiological level. Doses above 3 to 5 mg lead to serum melatonin concentration levels that are several times greater than physiological concentrations. Moreover, experimental studies indicate that the low doses of melatonin equal to 0.3 mg, when applied early, even 6,5 hours prior to DLMO, are as effective in advancing sleep phase as high doses [37]. On the other hand, supporters of higher doses of melatonin suggest that in clinical practice it is difficult to expect that patients will take melatonin earlier than 3 hours before their usual bedtime and will avoid light exposure. In addition, patients with comorbid somatic, neurological, and mental disorders are less responsive to the chronotherapeutic interventions than the healthy individuals. Lack of a rapid effect often leads to the premature termination of the treatment. Therefore, considering that melatonin is safe to use, the treatment of DSWPD, N24SWD and ISWRD should be initiated with a dose of 5 mg, as demonstrated in a randomized clinical trial [38]. This is particularly important in the presence of comorbid neuropsychiatric diseases or when patients are only partially compliant with behavioral interventions. After obtaining an improvement of the sleep rhythm, which occurs usually after 6 to 12 weeks of treatment, the dose can be lowered from 5 mg to 0.5–3 mg. If necessary, these 6–12 week cycles of higher melatonin doses can be repeated several times a year. However, it is recommended to avoid a continuous administration of high doses of melatonin for several months, because of its possible impact on sex hormones [39]. Another important principle is to use melatonin in high doses (up to 5–10 mg) only when it is administered at least 6 hours before the MSF. If the time of melatonin administration only slightly precedes or even follows MSF, e.g., in patients with ASWPD, in night shift work disorders, or during time zone changes, low doses (0.5 to 1 mg) are recommended. Administration of a high dose of melatonin late in the evening extends its action to the second half of sleep and even to the time after the final awakening. This causes a delay instead of the phase advance of the sleep-wake rhythm and can also impair physical and mental performance during the first hours of wakefulness. The principles of using melatonin and light therapy are shown in the Table 2.

Table 2. **Principles of the melatonin and light therapy in CRSWD**

Disorder	Chronotherapy recommended on the basis of the results of research	
	Melatonin	Light therapy
DSWPD	Doses of 0.5–5 mg before DLMO; when DLMO is unknown at least 6–7 hours before MSF (earlier administration of the drug may be even more effective, but in the clinical practice it is hardly applied due to a poor patient compliance). In the first 6–12 weeks of the treatment a higher dosage (5 mg) is preferred, and in a case of the comorbid neuropsychiatric diseases the used doses can be as high as 10 mg/d.	Exposure to the light 2,500–10,000 lux for 30 minutes to 2 hours, depending on the light intensity in the morning; the beginning of exposure 1–2 hours before the natural time of awakening. Improved effects may be obtained with blue enriched light. Avoiding intensive light (particularly blue enriched light) in the evening and at night is recommended.
ASWPD	Melatonin administration is not a treatment of the first choice. Administration of the low-dose of an immediate-release melatonin (0.5–1 mg) after waking up, or the use of a slow-release melatonin in a dose of 2 mg, just before going to sleep should be taken into consideration.	Exposure to the light 2,500 lux for 2 hours in the evening (e.g., from 7 to 9 p.m.); avoidance of an intense light in the morning after waking up.
N24SWD and ISWRD	Initially, 3–10 mg of melatonin, 1–2 hours before bedtime. After 6–12 weeks of the treatment a dose reduction to 0.5–3 mg in order to preserve the sleep rhythm consolidation.	Exposure to the light 2,500–10,000 lux for 30 minutes to 2 hours, depending on the light intensity in the morning (blind patients excluded).
Shift Work Disorder	After returning home from the night shift, application of a low melatonin dose of 0.5–3 mg is suggested. During the days off from the work and the transition to an earlier shift, a melatonin dose of 3–5 mg approximately 3 hours before the planned bedtime is recommended, especially when the falling asleep is difficult.	Exposure to bright light during the first half of the night shift is suggested. Two hours before the end of the night shift, light intensity should be reduced. While traveling home after the night shift, the dark sunglasses should be used to avoid an exposure to the intense sunlight.

table continued on the next page

Jet Lag Disorder	WEST FLIGHTS	
	After landing, 3–5 mg of melatonin one hour before going to sleep, which should be as late as possible, is suggested. Alternatively, use a low dose of melatonin (0.5–1 mg) in the second half of night in the case of too early morning awaking. Continue for several days.	Two or three days before traveling, the sunlight should be avoided in the morning, while increased exposure to bright light and physical activity late in the evening is recommended. After landing, an exposure to the bright light in the morning and avoiding the light in the evening is suggested.
	EAST FLIGHTS	
	For a period of 2 to 3 days before traveling, 3–5 mg of melatonin at least three hours before bedtime is suggested. After landing, the same treatment one hour before bedtime, continued for several days is recommended.	Two or three days before traveling, exposure to light of high intensity in the morning after awakening, but the evening light avoidance is suggested. After landing, avoidance of the intense light in early morning hours is recommended. Exposure to light in late morning and afternoon is also recommended.

DSWPD –Delayed Sleep-Wake Phase Disorder; ASWPD – Advanced Sleep-Wake Phase Disorder; N24SWD – Non-24-Hour Sleep-Wake Rhythm Disorder; ISWRD – Irregular Sleep-Wake Rhythm Disorder

Melatonin is considered a safe medicine and it does not interact adversely with other drugs [31], although fluvoxamine, citalopram, omeprazole and lansoprazole increase the blood melatonin level. The most severe side effect of melatonin used in the chronobiologcal treatment of CRSWD is the worsening of sleep disorders when the drug is administered during an inappropriate time of a day. Taking high doses of melatonin late in the evening may cause sleepiness and impairment of the ability to drive use machines. Possible side effects of melatonin are: headaches, dizziness, nausea, and sleepiness. The maximal recommended dose (10 mg/d) should not be exceeded, due to the inhibitory effect of melatonin on sex hormone secretion [39]. High doses (5–10 mg) should be used in short-term interventions, up to several weeks. Then, the doses have to be diminished (to 0.5–3 mg), particularly in young patients, and the use of melatonin progressively terminated (this last recommendation does not apply to the treatment of insomnia in patients above the age of 55 and among the blind). In the case of CRSWD recurrence, treatment with melatonin can be repeated every few months for a period of several weeks. Strict compliance with the principles of behavioral interventions allow for long breaks in melatonin administration, with no need for continuous treatment.

In the United States and Japan, agonists of melatonin receptor MT1 and MT2 are recommended in the treatment of the insomnia and circadian rhythm disorders [40]. Ramelteon (Rozerem; 1–4 mg) is used in the sleep onset insomnia and taken 30 minutes

before the scheduled patient bedtime. Tasimelteon (Hetlioz; 20 mg) is used to treat N24SWD in blind people and administered 30 minutes before the scheduled bedtime as well. The side effects of both drugs, such as sleepiness, dizziness, and fatigue, were observed in approximately 5% of patients and nightmares in a few cases. Moreover, tasimelteon causes an increase in the alanine transaminase (ALT) levels and in the frequency of the urinary and upper respiratory tract infections. Both drugs can cause allergic reactions as well. Agomelatine (Valdoxan, 25–50 mg), a melatonin receptor MT1 and MT2 agonist and serotonin 5HT2 receptor antagonist, registered in Poland, is recommended to treat sleep disorders in the course of depression [41]. It can also be used in the treatment of sleep disorders in blind people. Due to rare cases of liver damage reported with agomelatine treatment, the levels of transaminases (ALT, AST) should be monitored after 3, 6, 12, and 24 weeks of its application and even later, when clinically indicated.

Light therapy

Light therapy is a treatment method in which the therapeutic effect results from exposure to bright light. It is considered the method of choice for the treatment of seasonal affective disorder (SAD) and is often used to treat circadian rhythm disorders [42]. Using bright light just after waking up, and more preferably in the last two hours of the sleep period, causes a circadian phase advance while the light therapy administered in the evening causes a circadian phase delay. Influence of light on the circadian rhythms is better seen when the exposure to light matches the time of a core body temperature minimum, which normally occurs around 3 hours before the end of a patient's usual sleep period [43].

Apart from the time of exposition, the therapeutic effect of light therapy depends on the light intensity and the duration of exposure. For lamps with light intensity of 2,500 lux, the recommended exposure duration is generally two hours, while for those with light intensity of 10,000 lux, the exposure duration lasts 30 minutes. During the session, the patient should keep their eyes open (but does not have to stare at the lamp), and should be facing the light source directly and keep a distance from the lamp as recommended by the manufacturer. In clinical practice, patients might not routinely follow instructions as meticulously as seen in research. For this reason, the effectiveness of light therapy in clinical practice is usually lower than that observed in empirical studies [42].

A bright white light is typically recommended in light therapy. In the morning, it is preferable to use light with a higher intensity (usually 10,000 lux for 30 minutes), while in the evening a lower intensity light with an extended exposure period (e.g., 2,500 lux for 120 minutes). Light therapy duration usually lasts 2–4 weeks. There are no experimental data that confirms a greater efficiency of lamps from a specific length of the light spectrum (e.g., blue light) on associated sleep and mood disorders, mainly SAD. However, some findings indicate a desirable use of blue enriched light used in

light therapy of CRSWD. It has been demonstrated that the retinal photoreceptors, involved in the regulation of the circadian rhythm, containing melanopsin are most sensitive to blue light with a wavelength of 480 nm. Studies involving the measurements of blood melatonin have demonstrated, however, that light with a wavelength in the range 446–477 nm, with a maximum around 460 nm, exerted the strongest inhibitory effect on melatonin circadian rhythm in humans [44, 45]. The ultraviolet light has to be completely excluded due to its harmful influence on the eyes and skin. Although the blue enriched light seems to be more effective in the CRSWD treatment than white light, it is less safe and referred to as the "blue light hazard". Therefore, the norms regarding the intensity of blue light have to be strictly followed.

Light therapy is a safe and generally well tolerated method of treatment of sleep disorders. Possible side effects include fatigue, eye irritation, blurred vision, headache, anxiety, nausea, and sleepiness, which are usually mild. More serious side effects of light therapy reported in mood disorders was a phase change, from depressive to manic, and serotonergic-type side effects in patients receiving treatment with serotonin reuptake inhibitors (SSRI) [46]. Light therapy is relatively contraindicated in patients with some eye diseases and vision disorders. It is important to note that light therapy improves the energy and motivation at first and mood afterwards. Such a clinical effect in patients with suicidal thoughts may increase the risk of suicide attempt.

Apart from establishing the light treatment schedule with a patient, it is also important to explain in what part of a 24-hour period he/she should avoid artificial light, especially emitted by computer monitors, TV screens, tablets, and smartphones. People with DSWPD should not use such devices 3 hours before their usual bedtime, and not stay in brightly lightened rooms as well. On the other hand, patients with ASWPD should not switch on electric light after awakening at night, because it may result in further phase advance of their sleep-wake rhythm. Lastly, patients with endogenous CRSWD should be advised to avoid watching television at night.

Recapitulation

Disorders of the sleep-wake circadian rhythm have a strong negative impact on human health and functioning. The above described guidelines present the methods used to assess the patient's circadian rhythms in everyday clinical practice. To achieve this goal, patients should be advised to keep a sleep diary/log for at least 14 days. This enables not only an accurate description of the sleep-wake rhythm, but also to appropriately select a type of chronotherapeutic intervention and adjust the therapeutic approach to the circadian phase of a particular patient. In the treatment of CRSWD, melatonin and light therapy exert a proven therapeutic effect, but without the behavioral interventions their efficacy is substantially reduced. In the case of treatment with melatonin, setting the right time of drug administration is crucial. For instance, in DSWPD, melatonin should be administrated many hours before the planned bedtime.

Appropriate dosage of melatonin is also important. In patients with CRSWD, the use of higher doses for a short period (6 to 12 weeks) is usually preferred, and in those with neuropsychiatric disturbances even higher dose of 10 mg/d is recommended. In the case when treatment with melatonin has to be continued for a long time, a substantial reduction of the dose to 0.5–1 mg/d should be considered. Moreover, termination of the treatment has to be taken into consideration because of the possible inhibitory effect of melatonin on sex hormone, and the recommended doses should not be exceeded, particularly in young people. Among many available melatonin formulations, only those subjected to the most strict quality control, i.e., registered as prescription drugs or over the counter drugs should be used for therapeutic purposes. Light therapy is a method with high efficacy in research protocols and usually less efficient in clinical practice. Patients should be educated about the principles of light therapy, adequate duration of the treatment, and its application at the same time every day for the recommended period. The patient should also be aware of the need to keep the proper distance from the light source and to sit down always in front of the lamp with the whole face turned toward it, but without having to stare at the light. Treatment with the melatonin and bright light should be combined with the avoidance of light in the times of day crucial for the circadian rhythm regulation. Being in a brightly lightened room, watching TV, or using devices with light emitting panels late in the evening and at night (in DSWPD) or at early morning (in ASWPD), are the common causes for chronotherapy failure. Due to the frequent, partial compliance with behavioral interventions by patients, melatonin doses used in clinical practice are generally higher than those used in the scientific research.

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