Circadian Rhythm Sleep–Wake Disorders

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This group of diseases is characterized by a lack of synchronization of the intrinsic circadian rhythms with light–dark alternation. Either the intrinsic pacemaker itself is disturbed or the sleep–wake rhythm deviates from a normal intrinsic circadian rhythm because of external factors. Insomnia or hypersomnia complaints, or both, are the consequence. If the patient is able to adapt the sleep times to the inner rhythm, sleep duration and quality as well as the performance in the awake phase are normal. Sleep–wake disorders occur most frequently in shift workers, with negative effects on health and impaired performance at work. Sleep diaries are the basis for diagnosis, and the strict adherence to defined bedtimes in combination with light therapy are the basis for therapy.

6.1 Basics and Diagnosis

A disorder of the circadian sleep–wake rhythm is diagnosed when the intrinsic circadian rhythm of an individual cannot be synchronized with the light–dark alternation or social zeitgebers. This lack of synchronization may be caused by a disorder of the intrinsic pacemaker itself or may be a mostly behavior-related deviation of the sleep–wake rhythm of a normally working circadian rhythm.

The complaints may be of an insomnia (see ► Chap. 3) as well as a hypersomnia (see ► Chap. 5) nature, often even occurring in phases in the same individual, and they have to prevail for at least 3 months. Performance at work, social contacts, and the person's private activities are severely impaired. If the patient can choose his sleeping times according to his intrinsic rhythm, his sleep is restorative, and performance during the wake times is normal.

In most cases, the affected individuals may clearly name behavioral deviations of the day–night rhythm when they are asked directly. By means of a sleep diary that is generally required (see ► Sect. 2.3) for at least 1 week, or better 2 weeks, a suspected diagnosis can be made that has to be confirmed by actigraphy (see ► Sect. 2.4) for at least 1 week eventually. An assessment with and without social contacts (e.g., work, school) may be helpful. Morning- and evening-chrono type individuals can be evaluated by means of a publicly available and validated morningness/eveningness questionnaire (MEQ) according to Horne and Östberg. In doubtful cases, measurement of the core body temperature and melatonin profile may be required. In those cases, it is important to avoid social time givers during measurement. Polysomnography (PSG) is useful in unclear cases when other diseases, for example, sleep-related breathing disorders (see ► Chap. 4), are assumed.

For therapy of circadian rhythm sleep disorders, see ► Sect. 6.7.

Practical Tip

The most important diagnostic procedure in the context of suspected circadian rhythm sleep–wake disorders is a sleep diary for at least 1 week, or better, for 2 or more weeks.

6.2 Sleep–Wake Phase Disorders

This family of rhythm sleep–wake disorders is characterized by a significantly shifted sleep phase compared to the socially common circumstance that makes it difficult or even impossible to fall asleep or wake up at desired times. If the affected individuals are allowed to sleep according to their needs, they reveal a time-shifted but stable sleep–wake rhythm with normal sleep duration and quality. The shift is usually longer than 2 h. The shifted sleep phase has to be confirmed for at least 1 week in the sleep diary, completed by actigraphy if needed. This shift also manifests in the core body temperature graph and melatonin concentration.

6.2.1 Delayed Sleep–Wake Phase Disorder

The leading symptom of those patients is most commonly *insomnia*, because they go to bed at the usual times but are unable to fall asleep. Some patients can only fall asleep in the early morning hours so that they have to arise after only a short time asleep. Many patients complain of sleep inertia

and drowsiness in the morning and greatly impaired performance during the day. Characteristically, a performance peak is reported in the evening. If the biological clock is not considered, about half the patients show psychosomatic symptoms such as flushing, headache, or orthostatic or gastrointestinal disorders; about one third have neurotic conspicuities. Frequently, alcohol or sleeping aids are applied in the evening and stimulant drugs during the daytime to cope with the disorder. Because their sleep deficit accumulates during the workweek, many patients sleep for the whole day on weekends or vacations, which leads to further cementing of the delayed sleep phase.

Typically, the first signs of the disease appear in *adolescence*, which often leads to poor school performance. The differentiation to behavior-related late bedtimes with consecutive sleep deficit may be difficult in those cases. In early adulthood, the complaints may disappear when a regular sleep–wake rhythm is entrained by the onset of the working life. If this training is not successful, the disorder remains lifelong. However, with increasing age, the affected individuals have less difficulty, in particular with getting up in the morning.

Delayed sleep phase disorders are observed in about 0.5% of the population; in cohorts of insomnia patients and during adolescence, an incidence of about 10% was reported. In approximately 40% of the cases, the family history is positive; a genetic component may be considered. So far, the pathogenesis of the disease remains unclear.

6.2.2 Advanced Sleep–Wake Phase Disorder

For diagnosis, an advanced sleep phase compared to the desired time of sleep onset is crucial, with high sleep pressure in the early evening and waking up early in the morning without being able to fall asleep again.

Nearly all affected patients are *morning-chrono type individuals*. They complain typically about extreme sleepiness between 6:00 PM and 9:00 PM and most often wake up between 2:00 AM and 5:00 AM. Even if they go to bed later, they cannot sleep longer, so that often a sleep deficit accumulates that patients try to overcome with stimulants, such as coffee. Because these individuals have their performance peak mostly in the morning, difficulties at work occur only rarely, but social life is impaired by the difficulty of participating in evening activities. Because of the wish to sleep as late as others in the morning, a psychophysiological insomnia may be conditioned. Regarding differential diagnosis, early bedtimes in older people because of the lack of social contacts and early awakening in the context of insomnia (see ▶ Chap. 3) or a depressive disorder (see ▶ Chap. 10) especially have to be differentiated.

A prevalence of 1% is assumed for middle and older age groups. The disorder manifests in most cases in the middle-aged group, rarely in childhood. With increasing age, it more often increases and is considered as a chronic disease. Both genders are affected with equal incidence. Often a family predisposition is seen that allows suspecting an autosomal-dominant inheritance. Mutations in the circadian clock gene hPer2 have been discussed. The pathogenesis of the disease has not yet been clarified.

6.3 Irregular Sleep–Wake Rhythm Disorder

Patients with irregular sleep–wake rhythm disorder complain about excessive daytime sleepiness, disorders of initiating and maintaining sleep, or even both. The diagnosis can be based on ICSD-3, when at least three irregular and unpredictable shorter sleep periods during the 24 h are revealed in the sleep diary or actigraphy over an interval of 7 days. The total sleep time per 24 h corresponds to the age.

The disorder is mainly found in individuals who lack *social schedules*. With increasing age and increasingly rare outdoor activities, reduced light during the daytime also leads to flattening of the endogenous circadian rhythm, which is seen in an amplitude reduction of the core body temperature. An irregular sleep–wake pattern occurs frequently in cases of bed confinement, mental retardation, and neurodegenerative diseases. In cases of demented patients, the term sundowning is used when they show increased activity at the time of sundown.

The disorder has to be differentiated from an arbitrarily irregular sleep–wake pattern resulting from a lack of sleep hygiene.

6.4 Non-24-Hour Sleep–Wake Rhythm Disorder

When the internal clock shows a constant duration that, however, cannot be synchronized with the 24-h rhythm, intermittent insomnia or hypersomnia complaints occur. Thus, the disease is also called free-running sleep-wake rhythm disorder. Sleep diaries or actigraphy over at least 14 days show how the sleep period shifts every day at a constant interval. This shift, which mostly amounts to 1 to 2 h, can be objectified by measuring the core body temperature or determining the dim light melatonin onset.

Patients observe a regularly changing complaint pattern when they try to entrain the 24-h cycle. If the endogenous sleep phase is in the morning or in the afternoon, patients present symptoms comparable to delayed or advanced sleep–wake phase disorder. When the light–dark rhythm and the endogenous rhythm are synchronized for some days, the affected individuals are free of complaints. Some patients adapt their daily routine to their internal rhythm to avoid the consequences of nonrestorative sleep.

About half of all *blind people* suffer from this disorder (see ► Sect. 1.5). However, the onset cannot be correlated with the date of loss of sight. People who are blind from birth can be affected throughout their whole lives. Sighted individuals are only rarely affected, and when they are, this is often preceded by a longer isolation from zeitgebers or a chronotherapy (see ► Sect. 6.7) because of delayed sleep–wake phase disorder. Also, fluid transitions to delayed sleep–wake phase disorders are observed, which is seen in changing appearances of the disorder over longer periods.

6.5 Sleep Disorders in Cases of Jetlag or Shift Work

6.5.1 Sleep Disorder in Cases of Jetlag

When insomnia or hypersomnia complaints with impaired alertness during the day occur after a flight of at least two time zones, this is called jetlag. Additionally, somatic symptoms are reported such as gastrointestinal complaints or general discomfort.

The endogenous rhythm can shift about 60 to 90 min per day, but not all body functions are able to adapt to the new time zone with the same pace. The heart rate and sodium concentration, for example, adapt rapidly. Sleep structure, body temperature, and adrenalin secretion adapt more slowly and cortisol and potassium concentration extremely slowly. This internal dissociation of the endogenous rhythms is not noticed by many people, but it can impede maximum performance.

After flights to the east, disorders of initiating sleep occur, whereas with flights to the west rather disorders of maintaining sleep are observed. The problems mostly become apparent in the second night in the new time zone because in the first night the sleep deficit that developed during the flight is reduced. In addition, daytime sleepiness and reduced performance as well as urination at night, disturbed appetite, constipation, or diarrhea are observed. Because of frequently recurring changes of time zones, the flying staff of intercontinental flights is particularly affected.

The complaints are the more pronounced the more time zones are passed, the more often this happens, and the less the individual concerned is able to adapt to the new time zone. Evening-chrono type individuals, young people, and people with a rhythm with low daytime amplitudes find it easier to adapt. The complaints, however, are always self-limiting and thus have a primarily benign character.

It is easier to cope with flights to the west than with flights in the eastward direction because most people have an endogenous sleep–wake rhythm that is slightly longer than 24 h (see ► Sect. 1.5). In flights to the west, it is necessary to stay awake longer relative to the inner clock. With the increased sleep pressure, falling asleep is then easier, but according to the inner clock, at the destination one wakes up in the early morning hours. This longer waking phase is generally associated with increased sleepiness. In severe cases, one or two shorter sleep periods are recommended to compensate for the increased sleep pressure.

In the context of flights to the east, often difficulties of initiating sleep develop because, in relationship to the inner clock, at the destination one needs to fall asleep earlier, that is, without sufficient sleep pressure. In those cases, it may be reasonable to transitorily apply a hypnotic agent or to refuse to sleep in the first night at the destination.

In this way, the sleep pressure is increased for the following night, and acclimatization to the new light–dark rhythm at the destination is facilitated. For compensation of the sleep pressure that is increased by the prolonged waking phase, short sleep periods also may be recommended.

6.5.2 Sleep Disorder in Cases of Shift Work

When shift workers complain about insomnia or hypersomnia that recurs in timely association with night shifts, a shift work sleep disorder may be diagnosed. To confirm such an assumption, the complaints have to be present for at least 3 months, and the timely correlation to shift work has to be proven by a sleep diary (for at least 14 days), possibly combined with actigraphy.

In the European Union, 18.5% of employees are shift workers; night work is performed by 7.8%. Up to 32% of these shift workers with night shifts complain about sleep disorders that persist in about three fourths of the affected people even after ceasing shift work. A prevalence of shift work sleep disorders is assumed for 1% to 4% of the overall population. The present data on the impact of shift work on sleep and daytime alertness, but also the general health condition, are either based on small case numbers or studies with low evidence or the results are contradictory. Thus, no clear answers can be given on most of the specific questions.

There are different working time models of shift work. Under sleep medical aspects, in particular night work and alternating shift systems with night work are relevant. Alternating shifts can rotate forward (i.e., from early shift via late shift to night shift) or backward, as well as changing rapidly or slowly. Permanent night shifts seem to be associated with fewer sleep disorders than alternating shift systems with night shifts. Rapidly rotating shift systems seem to favor a changed sleep duration. After night shifts, shorter times of sleep are found; after late shifts they are rather prolonged in comparison to those of people with regular night sleep. There are suggestions that the percentages of light and REM sleep are reduced, although the deep sleep remains the same. Complaints in the context of shift work are generally similar to those of jetlag, and affected people may even lose their jobs. This problem is caused by the accumulated sleep deficit as well as the recurring need to adapt the inner rhythm. People who are able to relax easily more rarely suffer from sleep disorders in the context of shift work. Especially during night shifts, mental performance is severely impaired at times, and thus also the risk of mistakes and accidents is increased. During night shifts, morning-type individuals accumulate a particularly large sleep deficit because they wake up too early. Evening-type individuals reveal increased sleepiness and impaired performance during early shifts because they cannot advance their sleep pattern.

In the context of severe insomnia, incapability to perform shift work of particular shifts may exist partly until the complaints are sufficiently treated, which also applies for cases of restless legs syndrome that are difficult to treat. In case of sleep-related breathing disorders, generally no incapability to perform shift work is observed; however, in single cases severe insomnia may develop as consequence of device-related therapy, which may also lead to partial shift incapability until satisfactory treatment is achieved. Typically, people suffering from narcolepsy are not capable of performing shift work.

Long-term shift work per se seems to contribute to the genesis of a metabolic syndrome but less to cardiovascular or gastrointestinal diseases. The concern that even breast cancer may be associated with shift work could not be confirmed by a meta-analysis.

6.6 Circadian Sleep–Wake Disorders Not Otherwise Specified

If a circadian rhythm sleep disorder with insomnia or hypersomnia complaints (see ▶ Sects. 6.2, 6.3, and 6.4) cannot be allocated to one of the aforementioned diagnoses, it is classified in this group. The complaints are mostly associated with organic or psychiatric diseases. In the diagnosis, this aspect has to be mentioned specifically. Typical examples are dementia that in some cases shows an inverse sleep–wake behavior with sleep phases during the day and nighttime wandering as well as hepatic encephalopathy, where often a pattern similar to the delayed sleep–wake phase syndrome is found. In the context of Parkinson's disease, all these various disorders may be observed.

6.7 Therapy

The observation of *strict bedtimes* combined with *light therapy* is meanwhile an established therapy of rhythm sleep–wake disorders in sighted individuals.

Light is applied in the morning immediately after getting up. Only in cases of advanced sleep–wake disorders light therapy is applied in the evening. The exposure to daylight suppresses the melatonin discharge and thus synchronizes the inner clock. At least 2,000 lux are applied for a duration of 2 h; with 10,000 lux, the duration can be reduced to 45 min. Patients have to turn their face to the light source and maintain a distance of approximately 1 m.

Melatonin is applied at a dosage of 3–5 mg at a time that assures the overlapping of the endogenous and exogenous melatonin maximum.

- In cases of delayed sleep phase disorders, irregular sleep–wake patterns, and free-running rhythm, melatonin is applied about 4 h before turning off the light.
- In cases of advanced sleep phase disorders, melatonin is not indicated.
- In cases of jetlag, 4 days before arrival melatonin may be administered at the time that corresponds to the sleeping time at the place of destination.

Tasimelteon, which is a melatonin receptor agonist, received FDA approval in 2013 and EU approval in 2015 for the treatment of completely blind patients with non-24-h sleep–wake rhythm disorder.

Two clinical trials with 104 participants revealed that treatment with tasimelteon led to longer night sleep duration and shorter daytime sleep duration in comparison to placebo treatment. Most frequently reported side effects were headaches, increased hepatic enzymes (alanine aminotransferase) in the blood, nightmares or strange dreams, disturbed night sleep, infections of the upper airways or the urinary tract, and sleepiness.

The agent tasimelteon may impair activities that require complete mental alertness. So, tasimelteon should be taken every night at the same time, about 30 min before going to sleep. After intake of the drug, activities should be limited.

Also, 1.5–3 mg *activated vitamin* B_{12} (methyl cobalamin) has shown good success in the context of delayed sleep–wake phase syndrome, irregular sleep–wake rhythm disorder and non-24-h sleep–wake rhythm disorder because it increases the sensitivity to light.

Generally, the intake of hypnotics is not recommended because in many cases these attenuate the amplitude of the endogenous rhythm and thus have rather negative consequences. Because of an unfavorable benefit–risk assessment, modafinil has not been approved for shift work sleep disorder by the European Drug Agency since 2011.

Chronotherapy means delaying the daily sleep phase of 2 to 3 h in certain intervals until the desired sleep time is achieved. It is applied to treat delayed sleep phase disorder, and usually it is accepted by patients as pleasant because it concurs with their long endogenous rhythm. However, it should only be applied in exceptional cases because this therapy may trigger a free-running disorder that is then very difficult to treat.

Simple *behavioral measures* may be helpful to support therapy. In this context, on one hand sports and exercise, as well as abstinence from alcohol in the wake phases, must be mentioned. On the other hand, noise should be minimized during sleep after night shifts. If this is not possible, quiet music or radio programs may improve sleep quality. It also seems helpful to plan one third of the individually usual sleep time before working and two thirds after a night shift.

In cases of *shift work*, the work schedule should take into consideration the phase situation of the workers. Morning-type individuals are not suitable for night shifts, and evening-type individuals are not suitable for early shifts. For most people, late shifts do not represent a problematic issue. Generally, older people have more difficulties adapting to shift work than younger ones. In many cases, diabetes mellitus, chronic gastritis, ulcer, thyroid, liver, cardiac, circulatory, pulmonary, and neuropsychiatric diseases including addiction, as well as preexisting sleep disorders are contraindications for employment in shift work. In the context of shift work, not more than three subsequent night shifts should be worked to avoid a modification of the endogenous rhythm of the affected individuals. Taking into consideration all effects on sleep and daytime sleepiness in the context of an overall assessment, rapid forward rotation is recommended. Accordingly, adapted shift schedules with sufficiently long rest periods between the shifts should reduce the morbidity of shift work as well as increase the performance and satisfaction of the workers.

During the night shifts, bright light in the working locations may help to improve the alertness of the workers. In the morning after the night shift, the retina should be protected against too much light by wearing sunglasses and having a dark bedroom to keep the rhythm displacement as low as possible.

In the US and in some other countries, although not in the European Union, modafinil is approved for treatment of sleep disorder in cases of shift work. One hundred milligrams (100 mg) modafinil is taken about 1 h before beginning the night shift to reduce sleepiness during the working time. The subsequent day sleep in the morning after the night shift is not additionally impaired.

Sleep disorders in cases of shift work are frequently associated with psychophysiological insomnia, which has to be treated as well (see ▶ Chap. 3), because in this way a significant attenuation of the complaints can be achieved in many cases. Recent studies with, however, only small case numbers could show the benefit of psychoeducative and behavioral therapy-oriented interventions for sleep disorders as a consequence of shift work.

Practical Tip

The basis of the treatment of rhythm sleep–wake disorders is the adherence to strict bedtimes in combination with light therapy.

6.8 Questions

1. Please list the characteristics of rhythm sleep–wake disorders.
2. Which diagnostic and therapeutic principles for rhythm sleep disorders do you know?
3. Please define the different rhythm sleep–wake disorders.

Further Reading

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