Chapter 3
Introduction to Circadian Rhythm Disorders

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Definition

The term "circadian rhythm sleep/wake disorders" is used to encompass a wide variety of maladies in which there is misalignment of the endogenous circadian rhythm and the light/dark cycle that give rise to various sleep-wake complaints [1]. The word "circadian" is derived from two Latin terms—"circa" meaning about and "diem" which means "day," hence "about a day" [2]. When this term is applied to physiologic conditions, the implication is that these rhythms would continue in this near-24-hour cycle endogenously, i.e., in the absence of exogenous factors [3]. When synchronized to environmental cues such as the light/dark cycle, or social/activity cycles, this process is termed entrainment [4]. Each factor that can adjust or entrain this circadian rhythm is identified as a *zeitgeber*, which is German for "time givers" [2]. The history and evolution of these terms and concepts are described in Chap. 1.

In previous iterations of the International Classification of Sleep Disorders (ICSD), dyssynchrony between the circadian rhythm and the accompanying environment was identified simply as a circadian *sleep* disorder; the term "wake" was added to the most recent iteration to draw attention to the additional impairments in daytime function [5]. They are thought to occur because either (a) the external environment is not properly synchronized with the internal circadian system (e.g., jet lag, shift work) or (b) the circadian system itself is misaligned with the external environment (e.g., delayed sleep phase, advanced sleep phase, etc.) [4]. The clinical presentation of these disorders, however, is also influenced by numerous environmental, physiologic, psychologic, and social factors.

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Two major protocols have been developed to evaluate circadian rhythms [3, 6]. The first is a constant routine, during which subjects are kept awake for 24–48 hours in constant dim light conditions. The second is a forced desynchrony protocol, during which subjects alter the timing of their sleep and wake periods to prevent entrainment, while still preserving a 2:1 ratio of wake/sleep. The duration of the allotted sleep periods can vary widely under such protocols depending upon the investigative goals, ranging from as short as 7 minutes for sleep alternating with 14 minutes for wakefulness up to even a 42-hour day (i.e., a 14-hour sleep episode coupled with a 28-hour wake episode). Such protocols "desynchronize" physiologic circadian rhythms from the sleep/wake cycle to permit isolated analyses and are described in greater detail in Chap. 2. Their implementation consumes considerable resources and thus are not practical for routine clinical use.

Extensive research has determined that the human circadian cycle is controlled by the suprachiasmatic nuclei (SCN), which serves as the central biological clock ("master clock") or pacemaker, and is located in the anterior basal hypothalamus [4]. Under "free-running" conditions (i.e., in the absence of any cues or entrainment factors), these nuclei have an endogenous rhythm that averages 24.18 hours (range 23.47–24.64) [7, 8], i.e., usually slightly longer than the 24-hour day [2]. This genetically programmed rhythm is sometimes referred to as "tau" [9]. Further studies have shown that this intrinsic circadian period is slightly shorter in women (24.09 hours ± 0.2 hours) compared to men (24.19 hours ± 0.2 hours), which may have implications for sleep duration, insomnia symptoms and other circadian rhythm sleep/wake disorders [10] (see Chap. 9). Consequently, to function adequately in a 24-hour day, these nuclei require constant resetting or entrainment. This is accomplished by exposure to various environmental cues which serve as zeitgebers. These cues can reposition the circadian cycle forward or backward, depending on the type, timing, and intensity of exposure [1].

The generation of this circadian rhythmicity within SCN cells, as well as other cells in the body, is largely determined by numerous genes that are carefully regulated. These processes are described in more detail in Chap. 1. Central to this process are the positive transcription factors CLOCK and BMAL1 [11]. These proteins exit the nucleus and heterodimerize to act as an "on" switch for the beginning of the day by reentering the nucleus and binding to enhancer box (E-box) promoter elements of the PERIOD (PER1, PER2, PER3) and CRYPTOCHROME (CRY1, CRY2) gene families to induce their expressions [12]. PER and CRY proteins accumulate over the afternoon and peak in the evening in the extracellular space, before being phosphorylated. PER proteins phosphorylated by casein kinase enzymes are marked for proteosomal degradation. However, degradation is inhibited if CRY binds to PER1/PER 2, and this heterodimer is stabilized by PER3. In this instance, this PER-CRY-CK phosphorylated multicomplex is translocated to the cell nucleus in order to exert negative feedback on the expression of the CLOCK/BMAL1 complex [6]. Because of their integral role in maintaining circadian rhythmicity, variations, mutations, and/or polymorphisms in these genes may be linked to subsequent increases or decreases in circadian period length, which may underlie the development of some circadian rhythm sleep/wake

disorders (Fig. 3.1) [12]. Circadian rhythm derangements have been implicated in a wide variety of disorders including cancers, mood disorders, neurodegenerative disease, cardiovascular diseases, endocrine difficulties, and gastrointestinal tract issues [3, 13].

Borbély initially proposed a two-process model to explain how the sleep/wake cycle is regulated, and this work laid the foundation for decades of additional research [14, 15]. The model proposes two theoretical primary influences, a longitudinal homeostatic drive, termed "Process S," and a circadian drive, termed "Process C." Normally the two work in concert to promote maximal wakefulness in

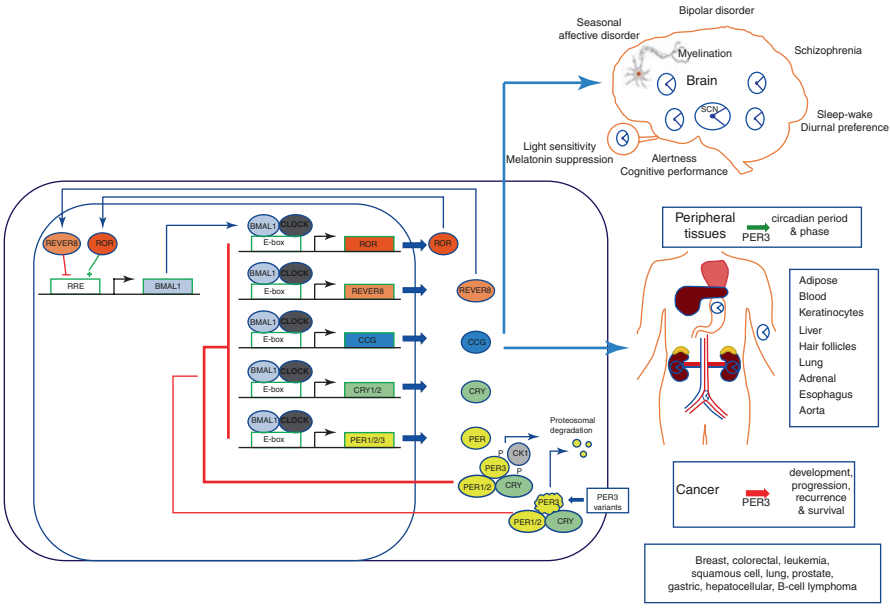

Fig. 3.1 The circadian clock consists of positive and negative integrated transcription and translation feedback loops. Transcription factors BMAL1 (also known as Arntl1 and Mop3) and CLOCK form a heterodimer that then binds to E-box motifs to promote the transcription of clock-controlled genes (CCGs), including CRY1/CRY2, PER1/PER2/PER3, REVERB and ROR, as well as others. CCGs go on to communicate the circadian timing period to a variety of other cellular processes throughout numerous peripheral tissues to maintain rhythmic cellular processes. The effects of CCGs may also underlie several circadian disturbances seen in numerous psychiatric disorders including mood and psychotic disorders, seasonal affective disorder, and diurnal preferences (circadian typology). ROR and REVERB proteins feedback and bind to ROR/REVERB response elements (RRE) to either enhance (ROR) or suppress (REVERB) expression of BMAL1. CRY and PER proteins dimerize in several combinations and subsequently translocate back into the nucleus to inhibit CLOCK/BMAL1 activity, resulting in autoregulation of PER and CRY, and other CCG activity. Alternatively, CRY/PER heterodimer proteins can also become phosphorylated by CK1 variants (e.g., CK1 delta, CK1epsilon) and thereby tagged for proteasomal degradation. Consequently, variants in PER and CRY genes can influence the stability of the circadian phase. For instance, PER3 variants (shown in the figure) can influence the expression of many CCGs and may underlie a wide range of phenotypes and disease conditions including numerous cancers. (Reprinted from Archer et al. [13], with permission from Elsevier)

the morning and increased propensity for sleep in the late evening. Process S posits a drive for sleep that increases with increased time spent in wakefulness [16]. An increase in adenosine over the course of a 24-hour period has been associated with an increased drive for sleep and likely is an important endogenous homeostatic sleep factor [17]. Other established markers include slow wave activity (SWA) in NREM sleep, as well as theta activity in wakefulness [11]. Only sleep can reduce this accumulated homeostatic drive [4]. While quality of sleep is driven by Process S, sleep quantity is more strongly influenced by circadian factors or Process C [16, 18]. This system has three components: the circadian oscillator in the SCN (approximating a rhythm of 24.18 hours), input pathways for other external/environmental stimuli (primarily light) to synchronize the SCN, and finally the output pathways from the SCN [4]. When properly aligned with Process S, this endogenous rhythm facilitates wakefulness during the day and continuous sleep at night. Subsequent to prolonged wakefulness, Process C will prevent sleep recovery at certain circadian phases, primarily during the second half of the waking day, and especially 2 hours before the habitual sleep onset time (sometimes referred to as "forbidden zones" or "wake maintenance zones"), even if homeostatic sleep drive is high (Fig. 3.2). These processes and their implications are described in greater detail in Chap. 11.

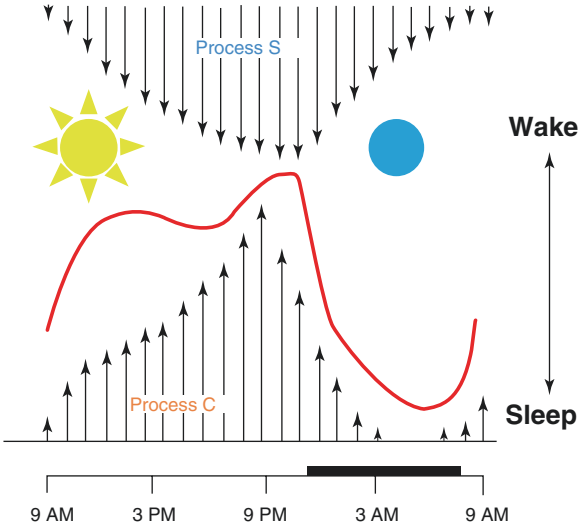

Fig. 3.2 Circadian oscillation (Process C) and homeostatic sleep drive (Process S) both influence the sleep-wake cycle. The red line indicates the wake propensity, with highest wakefulness seen at 9–10 PM and lowest wakefulness seen at approximately 6 AM. This illustrates that the circadian clock has a more powerful influence on wake propensity than homeostatic sleep drive. For instance, at 9 PM, although homeostatic sleep drive is strong, sleep does not readily occur because of the high level of alertness caused by the high circadian wakefulness signal. At approximately 6 AM, wake propensity is low despite the low homeostatic sleep drive, due to the trough in the circadian alerting signal. This figure appears in Chap. 11

The SCN receives external input primarily from the retina, which has specific photosensitive retinal ganglion cells that contain specialized photoreceptor cells with melanopsin. These cells, also known as intrinsically photosensitive retinal ganglion cells (ipRGCs), are distributed around the periphery of the retina. They are distinct from rods and cones, which are the visual cells. As a result, photosensitivity can be preserved even in conditions of visual loss [19]. Retinal physiology is described in greater detail in Chap. 14. These ipRGCs are most sensitive to light at a "short" wavelength of approximately 460 nm (450–480 nm (blue)) and least sensitive to "long" wavelengths of 595–660 nm (red/amber) [4, 19–21]. These cells convey photic input to the SCN via the retinohypothalamic tract, as well as to the pineal gland through the superior cervical ganglion [7].

The SCN also receives melatonin input from the pineal gland, which regulates its output. Efferent action on melatonin 1 (MT-1) and melatonin 2 (MT-2) receptors serve as darkness signals, sharply decreasing SCN activity. One of melatonin's functions, then, is to create a sleep permissive state during a limited time range. The timing of melatonin secretion, however, is regulated by output from the SCN and usually begins to rise approximately 2–3 hours before the natural sleep onset time, peaking in the middle of the sleep period [22]. Consequently, the onset of rise in melatonin levels under dim light conditions, also known as the dim light melatonin onset (DLMO), is one of several stable biological markers of circadian phase [22]. Operationally, this is defined when salivary melatonin rises above 2–3 pg/ml or plasma melatonin rises above 10 pg/ml (Fig. 3.3) [23, 24]. Melatonin production

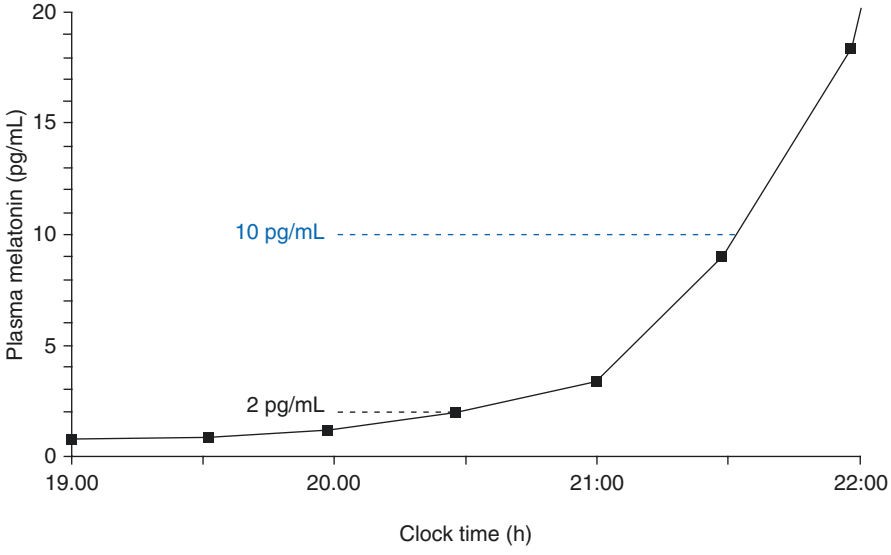

Fig. 3.3 The dim light melatonin onset (DLMO) in plasma is defined as the interpolated time when melatonin levels continuously rise above a threshold of either 2–3 pg/mL (3 pg/mL not shown) or 10 pg/mL (which usually occurs 1 hour later). In this figure, DLMO2 is approximately 2030 hours and DLMO10 is approximately 2130 hours. (Reprinted from Lewy et al. [23] (Open Access))

can be readily suppressed by light exposure through the retinal melanopsinergic system [25], beginning with light intensities under 200 lux, and more readily with light in the 460–480 nm wavelength [25]. Additionally, damage to the superior cervical ganglion, for instance, with cervical trauma, can also lead to lowered melatonin production and subsequent disruption of circadian rhythm [25].

Phase Response Curves of Light, Melatonin

Both light and melatonin can alter the circadian oscillator (SCN) and its subsequent output. Phase response curves (PRCs) of the circadian system for both light and melatonin have been derived. A PRC outlines the magnitude and direction of response (phase advance, phase delay, or neutral) of the circadian system to a zeitgeber for a given time. For a normally entrained person, light will advance the circadian rhythm if given in the early morning hours, while light will delay the rhythm if given in the evening hours [26]. Such findings have significant implications for accelerating entrainment to a new time zone or accommodating to shift work, for instance (see Chaps. 11 and 13 for more details; also see Fig. 3.4 for a diagram of typical phase relationships and Fig. 3.5 for an illustration of the PRC to light [27]).

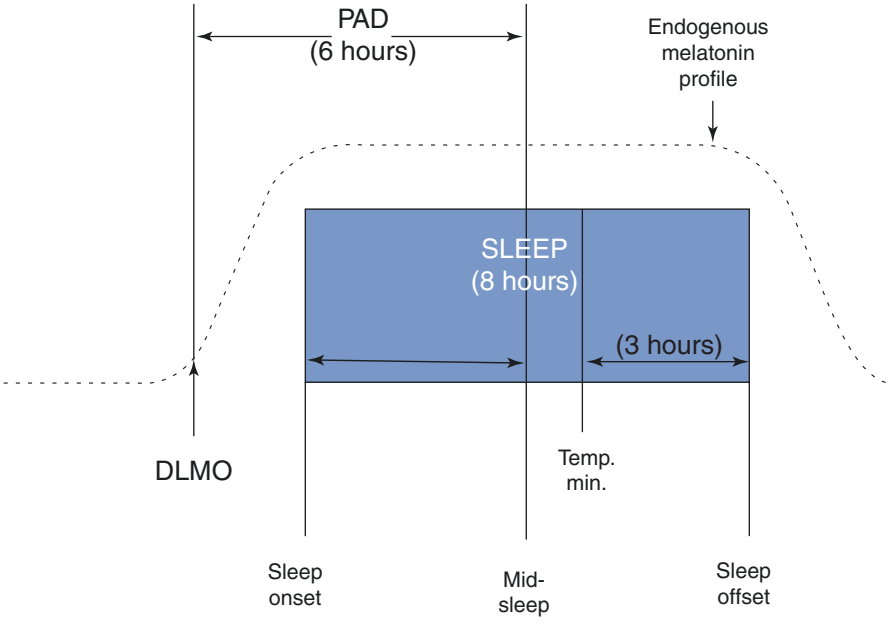

Fig. 3.4 Schematic diagram of normal phase relationships (rounded to the nearest integer) between sleep phase markers including dim light melatonin onset (DLMO), the endogenous melatonin profile, core body temperature minimum, and an 8-hour sleep time. The phase angle difference (PAD) is the hypothesized interval between the DLMO and mid sleep, shown as 6 hours in this figure, which is the average PAD for healthy controls. In patients with phase delay, for instance, the PAD would be ≤6 hours, while those who are advanced would have a PAD ≥6 hours. (Reprinted from Lewy et al. [23] (Open Access))

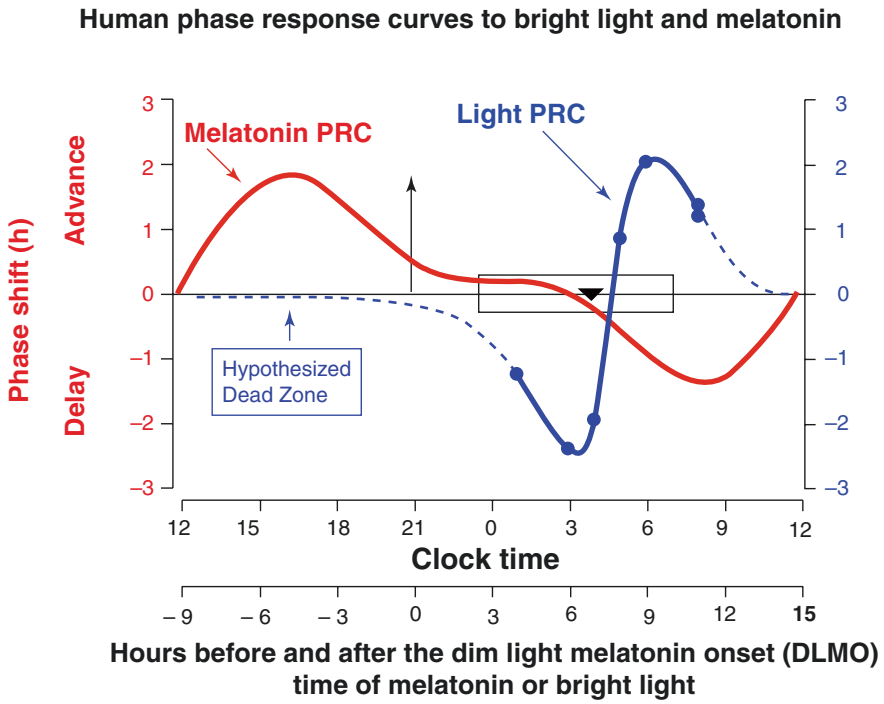

Fig. 3.5 Phase response curves for melatonin (shown in red) and light (shown in blue). The rectangle illustrates a hypothetical entrained sleep time of 7.5 hours, starting 2.5 hours after the DLMO (illustrated with ↑). The triangle shows the core body temperature minimum, 7 hours after the DLMO. These curves are derived from control subjects receiving melatonin doses of 3.0 mg per day or bright light pulses of 3500 lux at different times. Phase shifts are derived from circadian phase assessments conducted before and after 3 days of free running. (Reprinted from Eastman and Burgess [27], with permission from Elsevier)

The phase response curve of melatonin is approximately 180 degrees out of phase with the phase response curve to light, such that exposure in the late afternoon or early evenings will advance the sleep cycle with maximum advancement occurring when dosed ~5 hours before the DLMO [24, 28, 29]. Exposure in the mornings will delay the circadian cycle, though the amplitude of delay effect in the mornings is modest [5] (see Chap. 11 for more details, also see Fig. 3.5).

Chronotype (Circadian Typology) and Phase Tolerance

The term "chronotype," also known as circadian typology, is used to define individual preferences of sleep and wake times, with earlier chronotypes (sometimes called "larks") having preferences for earlier timing and later chronotypes ("owls") with preferences for later timing [30]. Approximately 40% of people display a

morning or evening chronotype, while the remaining 60% have a neutral chronotype [31]. Variations in chronotype are determined partially by polymorphisms in circadian genes [7].

An individual's ability to tolerate sleeping at an abnormal circadian phase is referred to as "phase tolerance." Phase tolerance will also determine to a limited extent the presence of a circadian rhythm sleep/wake disorder, since symptom presentation will vary depending on a person's ability to adapt to the light dark cycle, for which there is significant variation [32, 33]. Phase tolerance may decline with age according to some reports, but data are conflicting [26, 33]. These changes have many implications, particularly for shift workers (see Chap. 11), including health professionals (see Chap. 12).

Circadian Changes with Age

Mounting evidence indicates the circadian system is not static after infancy as was once believed. Increasing evidence suggests the endogenous circadian period and light sensitivity are altered in puberty, resulting in the development of a delayed sleep phase in adolescence [34]. Carskadon proposed that adolescents develop a resistance to sleep pressure and simultaneously develop a delay in the circadian phase, providing a drive to stay up later in the evenings and awaken later in the mornings [35]. This delay in circadian phase is correlated with secondary sex development, with girls showing a delay in timing 1 year earlier than boys, paralleling their earlier pubertal onset [34, 36, 37]. Men, however, show greater magnitude of changes in chronotype from adolescence to adulthood than women [37]. This delay in timing of sleep onset has been seen in adolescents in over 16 countries spanning six continents [37]. Moreover, animal studies across six different mammalian species have also shown a delay in circadian phase with puberty, suggesting this is a preserved mammalian developmental stage [34]. Further studies suggest that adolescents show a blunting of response to the phase advance effects of morning light and an exaggerated response to the phase delaying effects of evening light exposure [34]. Additionally, adolescents show a decreased accumulation of homeostatic sleep drive compared with prepubertal children, further enabling a delay in sleep onset [38]. These changes in the circadian system and homeostatic drive in adolescence have significant implications for interpreting sleep complaints of adolescent patients. For instance, delaying school start times for adolescents, in recognition of these biological circadian changes that occur with pubescence, has been shown to improve academic performance and reduce absenteeism, in addition to having other positive benefits for students (described in further detail in Chap. 7).

This delay in circadian timing reaches peak eveningness at approximately age 20 and then continues to gradually advance toward morningness in the ensuing decades [6, 39]. Morningness-eveningness scores (MEQ, see later in this chapter) have been shown to increase by 1 point every 3.8 years [40, 41]. Greater differences in chronotype are seen with gender in the second and third decade of life, with men

more frequently having later chronotypes earlier in life, but becoming earlier chronotypes after ages 40–50 [37, 39]. Variability in chronotype decreases significantly with age.

Responsiveness to light declines with age through a variety of factors. Aging is often associated with yellowing of the lenses of the eyes, which can result in decreased transmission of blue and green wavelengths due to decreases in lenticular transmittance [42]. Furthermore, there is a decrease in the number of photoreceptors within the circadian system although responsiveness to light is relatively preserved with age [42]. These factors may contribute to age-related circadian changes and subsequent development of circadian rhythm sleep/wake disorders, particularly advanced sleep phase wake disorder, in the geriatric population.

Epidemiology of Circadian Rhythm Sleep/Wake Disorders

Up to 3% of individuals may suffer from circadian rhythm sleep/wake disorders, but this number may be as high as 10% in adults and 16% in adolescents due to missed diagnoses or misdiagnoses according to some studies [43]. Other populations particularly vulnerable to the development of circadian rhythm disorders include the blind, as one in five experiences total absence of light perception [7]. In this patient population, prevalence estimates of circadian rhythm sleep-wake disorders are as high as 60–80% [7]. The International Classification of Sleep Disorders third edition (ICSD-3) identifies six major types of circadian rhythm sleep/wake disorders: advanced sleep phase type, delayed sleep phase type, irregular sleep/wake type, free-running type, jet lag type, and shift work type. Another common manual used for diagnosis is the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), which has similar criteria and diagnostic categories as the ICSD-3 [44]. The key criteria that all these disorders share is an inability to fall asleep and awaken at desired times, leading to functional impairment. All arise due to the misalignment between the circadian system and the 24-hour external environment.

Diagnosis of Circadian Rhythm Sleep/Wake Disorders

The International Classification of Sleep Disorders third edition (ICSD-3) recommends that clinicians should use caregiver reports, sleep logs, and/or actigraphy to assist with the longitudinal evaluation of such disorders, for at least 7 days, but ideally for 14 days or more [5, 44]. The addition of chronotype questionnaires such as the Morningness-Eveningness Questionnaire (MEQ), the Composite Scale of Morningness (CSM), or the Munich Chronotype Questionnaire (MCTQ) described below can be useful. If possible, the use of circadian phase markers such as salivary DLMO, core body temperature and/or other objective markers for circadian rhythm is encouraged, although their role as diagnostic tools remains uncertain. These

measures are described in detail in Chaps. 4 and 6. Such measures may also provide guidance regarding proper timing for administration of light and/or melatonin as treatment options [44].

Questionnaires

Several questionnaires are described in Chap. 5. Some of the most common chronotype questionnaires are the MEQ, developed by Horne and Ostberg in 1976, the CSM by Smith et al. in 1989, and the MCTQ, developed by Roenneberg et al. in 2003 [6, 45, 46]. The MEQ consists of 19 questions asking about the preferred timing of different daily activities, producing a composite score ranging from 16 to 86. Lower scores are suggestive of an evening chronotype, while higher scores suggest a morning chronotype. These scores will place subjects into one of five chronotypes: definite evening type (16–30), moderate evening type (31–41), intermediate (42–58), moderate morning type (59–69), and definite morning type (70–86) [43]. The CSM is a 13-item questionnaire derived partially from the MEQ as well as two other questionnaires, the diurnal type scale, and the circadian type scale [45, 46]. The MCTQ evaluates sleep timing on both work and free days to assess a person's chronotype. Another major difference with respect to the MEQ is that the MCTQ asks about actual sleep and wake times in addition to preferred timing of daily activities [43].

Actigraphy

Circadian rhythm disorders are routinely evaluated with actigraphy, a procedure utilizing the presence of body and/or limb movements to provide estimates of the sleep/wake schedule. These devices have been endorsed by the American Academy of Sleep Medicine (AASM) [47]. Data are typically obtained from devices worn on the wrist, but can also be worn on the ankle or waist to record movements through a piezoelectric or micromechanical accelerometer. Prolonged periods of data, usually weeks to months, can be recorded and later downloaded to an appropriate interface that can apply mathematical algorithms that produce temporal raster plots that ultimately provide sleep/wake estimates [47]. This technology is described in greater detail in Chap. 4. Commonly obtained sleep parameters include sleep onset latency (SOL), total sleep time (TST), wakefulness after sleep onset (WASO), and sleep efficiency (SE = TST/time in bed) [47]. Many actigraphy devices also have buttons that subjects can push to define certain events (e.g., bedtime), as well as light sensors that provide estimates of ambient exposure [47]. These data correlate well with sleep logs and caregiver reports, but actigraphy is completed more reliably [48, 49].

Treatment Options

Using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation), the American Academy of Sleep Medicine published recommendation statements for the treatment of circadian rhythm sleep-wake disorders in 2015 [5]. Interventions fall broadly into four main categories: (1) prescribed timing of sleep/wake activity and/or physical or social activities during the day; (2) light therapy and/or avoidance of light; (3) medications with chronobiotic effects and/or those that promote sleep or wakefulness; and (4) somatic interventions that alter body functions to ameliorate sleep/wake symptoms. The use of these modalities (if applicable) is discussed in each specific circadian rhythm sleep/wake disorder chapter, and select treatments are described below.

Light Therapy

Light therapy was first used in the 1980s when it was discovered that it could suppress melatonin production and alter circadian rhythms [50, 51]. Its efficacy on the treatment of circadian rhythm sleep/wake disorders can vary considerably depending on a wide variety of factors, including the luminosity of the light source, distance to light source, and the wavelength, timing, and duration of exposure. The brightness or luminosity of a light source is measured in lux (lx), a standard unit of light flow and measure of photopic illuminance. Higher lux is generally associated with higher efficacy for shifting circadian rhythms, but may impact compliance, particularly among older individuals [52]. Sunlight produces in excess of 100,000 lux, while indoor light typically is about 100 lux and rarely over 500 lux [53]. The threshold for suppression of melatonin had been previously assumed to be 2500 lux [53], but further work has described significantly lower lux as effective for melatonin suppression with longer exposure (e.g., <200 lux for 8 hours) [54] (see Chap. 15). Light therapy at >2500 lux administered before the core body temperature minimum (CBT_{min}) has been definitively demonstrated to delay the sleep/wake circadian rhythm, while light therapy after this will promote advances [55]. Consecutive days of exposure also affect the phase responses to light, as circadian resetting effects of light exposure can even be seen at 50 lux or lower [56]. As a result, chronic exposure to room light may have a greater impact than a few minutes of exposure to intense light.

The majority of light therapy devices emit fluorescent white light at 10,000 lux and contain ultraviolet light filters [57]. Additional monochromatic green or blue light-emitting diode (LED) light boxes are marketed with added benefits of portability and decreased intensity of white light, while purportedly preserving associated benefits, but evidence of equivalent efficacy has been inconsistent [58–60]. A common benchmark developed in the 1990s for therapeutic use of light therapy is 10,000 lux for 30 minutes a day, the timing of which depends on the nature of the disorder being treated [61]. For instance, timing will vary significantly for the

treatment of jet lag disorder (see Chap. 13). Common side effects of light therapy include insomnia, headaches, eye strain, nausea, irritability, and agitation [62]. Additional potential light therapy adverse effects are described in Chap. 6.

Melatonin

A 0.1–0.3 mg dosage of melatonin will produce plasma concentrations between 100 and 200 pg/ml, considered a physiologic level, while 1.0 mg would be predicted to produce supraphysiologic levels of 500–600 pg/ml [25]. Maximum plasma concentrations are typically reached 45 minutes after administration [25]. Melatonin's half-life is short, with immediate release melatonin ceasing its action within 90 minutes [63]. Considering that it is metabolized by cytochrome P4501A2, medications that affect 1A2 activity could alter the available blood concentration [25]. As of 2018, phase response curves for doses above 5 mg have not been published [5] and, as such, are not routinely recommended for the treatment of circadian rhythm sleep/wake disorders [25]. Most data suggest that timing of melatonin administration is more important than dosage [5]. In many countries, it can be sold as an over-the-counter supplement and is not considered to be a pharmaceutical product. As a result, it is not subject to the same degree of regulation as a prescription medication, creating questions of quality and purity [63].

Summary

Circadian rhythms play a pivotal role in multiple physiologic functions. As a result, dysregulation may lead to the development of circadian rhythm sleep/wake disorders, which can have significant impacts on physical and mental health. These conditions are frequently misdiagnosed or overlooked. Gathering an appropriate history should include a detailed discussion of the timing of sleep/wake patterns and social/work schedules. Utilizing additional diagnostic tools such as chronotype questionnaires and actigraphy can lead to enhanced recognition of these disorders. Understanding the regulation and control of the sleep/wake cycle will lead to the development of appropriate treatment plans, which incorporate both chronobiotic strategies and behavioral modifications.

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