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REVIEW

Circadian Rhythm Sleep–Wake Disorders: a Contemporary Review of Neurobiology, Treatment, and Dysregulation in Neurodegenerative Disease

Tyler A. Steele[1,2,7] · Erik K. St Louis[1,2,3,5] · Aleksandar Videnovic[6] · R. Robert Auger[1,3,4]

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Abstract

Circadian rhythms oscillate throughout a 24-h period and impact many physiological processes and aspects of daily life, including feeding behaviors, regulation of the sleep-wake cycle, and metabolic homeostasis. Misalignment between the endogenous biological clock and exogenous light–dark cycle can cause significant distress and dysfunction, and treatment aims for resynchronization with the external clock and environment. This article begins with a brief historical context of progress in the understanding of circadian rhythms, and then provides an overview of circadian neurobiology and the endogenous molecular clock. Various tools used in the diagnosis of circadian rhythm sleep–wake disorders, including sleep diaries and actigraphy monitoring, are then discussed, as are the therapeutic applications of strategically timed light therapy, melatonin, and other behavioral and pharmacological therapies including the melatonin agonist tasimelteon. Management strategies towards each major human circadian sleep–wake rhythm disorder, as outlined in the current *International Classification of Sleep Disorders – Third Edition*, including jet lag and shift work disorders, delayed and advanced sleep–wake phase rhythm disorders, non-24-h sleep–wake rhythm disorder, and irregular sleep–wake rhythm disorder are summarized. Last, an overview of chronotherapies and the circadian dysregulation of neurodegenerative diseases is reviewed.

Circadian rhythms impact a wide variety of physiological processes. The term circadian stems from the Latin words *circa*, for ("approximately, about"), and *diem* ("day"). Circadian rhythms oscillate with an approximate 24-h period and influence many aspects of daily life throughout the course of the day. The circadian system exerts prominent influence over daily feeding behaviors [1], regulation of sleep–wake cycles [2, 3], neuroendocrine hormonal release [4], and homeostatic and metabolic processes [5] such as autonomic control of blood pressure [4] and body temperature [6]. In its free-running state, the circadian rhythm oscillates with an innate period [7] termed *tau*, with an average duration of slightly longer than the 24-h light–dark cycle (24.18 h) among humans [8], although women have been observed to have a shorter period and a greater frequency than men of having a tau period that is shorter than 24 h [9]. The circadian system is entrained to the light–dark cycle and 24-h clock time of the current local environment via external stimuli called zeitgebers (*time-givers*). Zeitgebers include mealtimes, work schedules, exercise, and most notably, light exposure.

Endogenous circadian rhythms are increasingly challenged by modern lifestyles and culture with the ubiquitous presence of artificial lights, a large proportion of the population performing shift work, and a commonplace 24/7 work environment [10]. Circadian rhythm disorders emerge when the internal biological clock is not in sync with the external environment. Disruption of the natural circadian rhythm has been correlated with several adverse health outcomes, including cancer [11, 12], neurodegenerative [13] and cardiovascular diseases [14], type 2 diabetes [15], endocrine

✉ Erik K. St Louis
StLouis.Erik@mayo.edu

1 Mayo Center for Sleep Medicine, Rochester, Minnesota, USA

2 Department of Neurology, Rochester, Minnesota, USA

3 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Rochester, Minnesota, USA

4 Department of Psychiatry, Rochester, Minnesota, USA

5 Mayo Clinic Health System, La Crosse, Wisconsin, USA

6 Massachusetts General Hospital, Department of Neurology and Harvard Medical School, Boston, Massachusetts, USA

7 Rochester Technical and Community College, Rochester, Minnesota, USA

[11] and gastrointestinal disorders [16]. Chronotherapeutic approaches are also being developed to better harness and capitalize upon the complex interrelationships between endogenous circadian rhythms, physiologic functioning, and pharmacodynamic properties of therapeutic agents and to optimize treatment efficacy and minimize adverse effects [17]. Some examples across disease states of chronotherapeutic discoveries that enhance treatment outcomes include chrono-chemotherapy, where administration of cancer treatments in accordance with the biological clock can decrease toxicity and improve outcomes [17–20]; evidence that nighttime antihypertensive administration optimizes 24-h blood pressure control [21]; comparative trials showing chronotherapeutic strategies of once daily inhaled steroid therapy given between 1500 and 1730 h vs. typical QID dosing have comparable efficacy (presumably preventing the asthmatic inflammatory cascade that mediates nocturnal asthma and overall disease severity) [22]; and strategically administering higher evening doses of antiseizure medications in patients with nocturnal or early-morning seizures to improve their seizure burden and medication tolerability [22].

This review begins with a brief historical context of our understanding of circadian rhythms, then provides an overview of circadian neurobiology and the endogenous biological clock to provide context for understanding circadian disorders and appropriate treatment strategies. Diagnostic approaches and therapeutic strategies for the major circadian sleep–wake rhythm disorders are then reviewed, and finally, the interplay of circadian dysfunction, chronotherapy, and neurodegeneration is considered.

Historical Context of Circadian Rhythms

Biologically rhythmic behaviors were initially formally observed centuries ago. Jean-Jacques d'Ortous de Mairan discovered that circadian rhythms were endogenous rather than reactive to the surrounding environment, when he systematically experimented with the heliotrope plant species *Mimosa pudica* in 1729 and found that its leaves continued alternately folding and unfolding in a rhythmic fashion as they did in natural light–dark cycles even when kept in an environment of continuous darkness [23]. Modern circadian science began with the intensive experiments of Nathaniel Kleitman and his research assistant Bruce Richardson, conducted in isolation from light deep in Mammoth Cave, Kentucky. Paralleling the earlier work of de Mairan, they found that humans maintained an intrinsic sleep–wake and body temperature rhythm when unentrained from light, with a periodicity of slightly longer than 24 h [24]. Modern chronobiology was spearheaded by Drs. Colin Pittendrigh and Jurgen Aschoff, who described circadian rhythm manipulation by light and circadian response to external cues, respectively [25, 26]. Dr. Franz Halberg, a scientist and physician at the University of Minnesota, introduced the term *circadian* and began to apply these concepts clinically [17], helping establish the discipline of chronobiology [27].

Several key anatomic structures [28] of the circadian system have been identified including the retinohypothalamic tract (RHT) [29, 30], motivating further investigation toward the mechanisms of photic input and its influence on circadian rhythmicity, and the suprachiasmatic nucleus (SCN), the brain's master timekeeper, discovered in lesion studies using rats [31, 32]. More recently, the 2017 Nobel Prize in Physiology and Medicine was awarded to three American circadian scientists. Working with fruit flies, they uncovered the critical genetic underpinnings and transcription/translation cycle that governs the biological clock [33].

Circadian Neurobiology

The biological timekeeper required for optimally functioning circadian rhythmicity resides within the suprachiasmatic nucleus (SCN), which is comprised by two small paired nuclei in the anterior hypothalamus that each contain about 10,000 neurons [34]. The SCN Is the body's master timekeeper, governing key processes in circadian homeostasis, including the relaying of circadian signals from external stimuli, especially light, but also influenced by other external influences, the main zeitgebers of exercise and meal times [37] [35].

The light-dark detection pathway is mediated by the specialized intrinsically photosensitive retinal ganglion cells (ipRGCs) which transduct the influence of light-dark via the retinohypothalamic tract to the SCN, which in turn relays down via the intermediolateral cell column (IML) of the spinal cord before ascending to synapse within the superior cervical ganglion, and ultimately terminates at the pineal gland, thereby regulating the cyclic secretion of melatonin (see Fig. 1 [36]). ipRGCs are specialized retinal cells that contain the photopigment melanopsin, which is key for mediating phototransduction of light stimulating the circadian system [37–40], and which is distinct from the rods and cones. When these cells receive light stimuli, a cascade of depolarization initiates an action potential through the RHT which innervates the SCN. The core, or ventral SCN, is responsible for the sensory processes to detect light and dark, while the shell, or dorsal SCN, relays to the peripheral oscillators [4]. Once activated, the SCN directly innervates the paraventricular nucleus (PVN) of the hypothalamus. This connection is the only inhibitory location within the pathway and is inhibited by the presence of light in the 440–480-nm wavelength, corresponding to blue light on the visible spectrum [41]. Among other physiological functions, the PVN is an important control center that relies on input from the

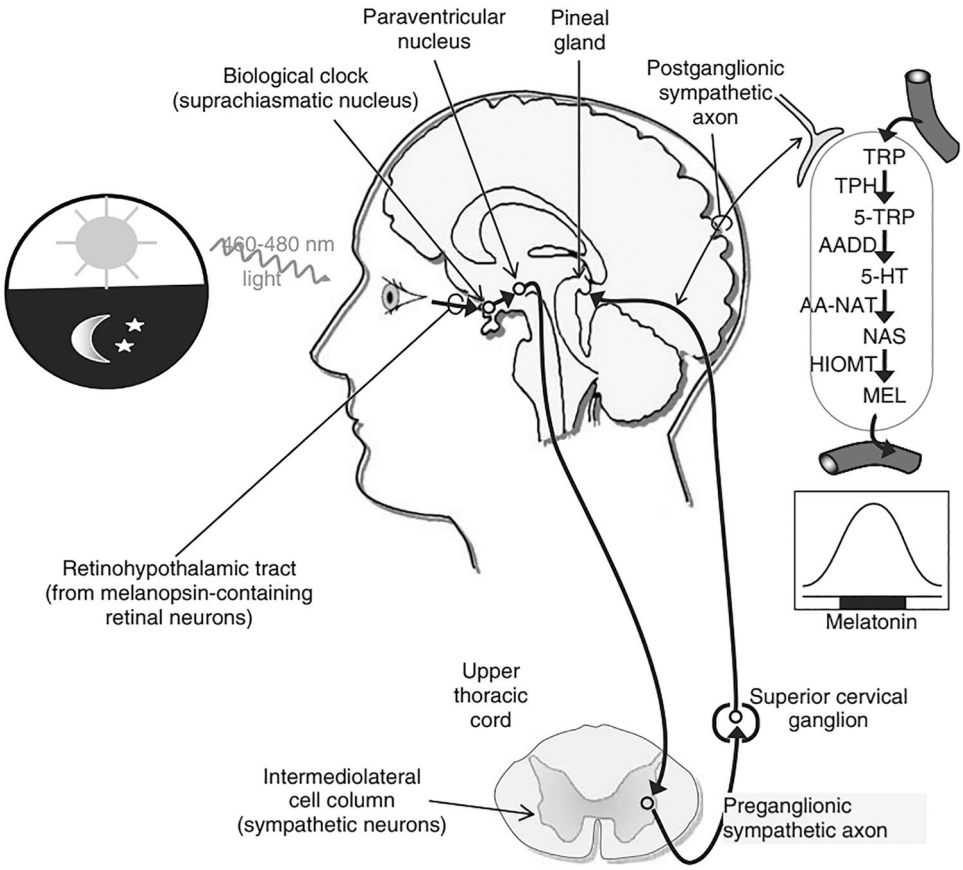


Fig. 1 Key neuroanatomical pathways of the circadian system. The light-dark detection pathway begins at the intrinsically photosensitive retinal ganglion cells (ipRGCs), activated by the presence of light with a wavelength of approximately 460 nm during the day. Light activates the pathway via the melanopsin-containing ipRGCs which phototransduces light stimuli into electrophysiological impulses that are further conveyed through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), the master biological timekeeper. Projections from the SCN mainly innervate the paraventricular nucleus, which travels down to the intermediolateral cell column and superior cervical ganglion (SCG). Noradrenergic SCG projections to the pineal gland activate melatonin secretion into the bloodstream. In the presence of light, the SCN provides an inhibitory (via ϒ-aminobutryiuc acid) signal to this pathway to suppress melatonin secretion. Conversely, glutamatergic output from the SCN to the PVN enhances melatonin synthesis and secretion during darkness. Figure reproduced and legend adapted from Korkmaz A, Topal T, Tan D, et al. Role of melatonin in metabolic regulation. Rev Endocr Metab Disord 2009; 10, 261–270

SCN and other sources to directly regulate organs like the heart, liver, and pancreas to manipulate autonomic processes and behaviors, such as heart rate rhythmicity or food intake [4]. Though major organ systems, and even individual cells [42], have biological clocks that function independently of the light-dark cycle [1], the SCN is necessary for the synchronization of peripheral rhythms [43]. From the PVN, the pathway continues by relaying down the neuraxis to the intermediolateral cell column of the thoracic spinal cord to the superior cervical ganglion, with noradrenergic signaling relayed to the pineal gland to effect melatonin release into the bloodstream. The entire pathway is shown in detail in Fig. 1.

Throughout the mammalian class, the biological clock is highly conserved [44]. The basic molecular genetic mechanism is the transcription-translation negative-feedback loop shown in Fig. 2 [45–47]. This process impacts the gene expression of many important processes in the body [44]. The most key transcription factors and genes of the core feedback loop within the biological clock include Brain and Muscle Aryl Hydrocarbon Receptor Nuclear Translocator-Like 1 (BMAL1), Circadian Locomotor Output Cycle Kaput (CLOCK), Period (Per) 1-3, and Cryptochrome (Cry) 1-2. Mutations to the genes of the molecular clock have consequences on normal circadian functioning. For instance, some cases of Familial Advanced Sleep Wake Phase Disorder (FASWPD) are associated with a Per2 mutation [48] and mice with Cry1 and Cry2 deletions have a completely chaotic circadian sleep–wake rhythm [49]. The molecular clock begins with CLOCK bound to BMAL1 to form a transcriptional activator on both the Cry and Per genes, which are activated during the biological daytime hours [50]. The

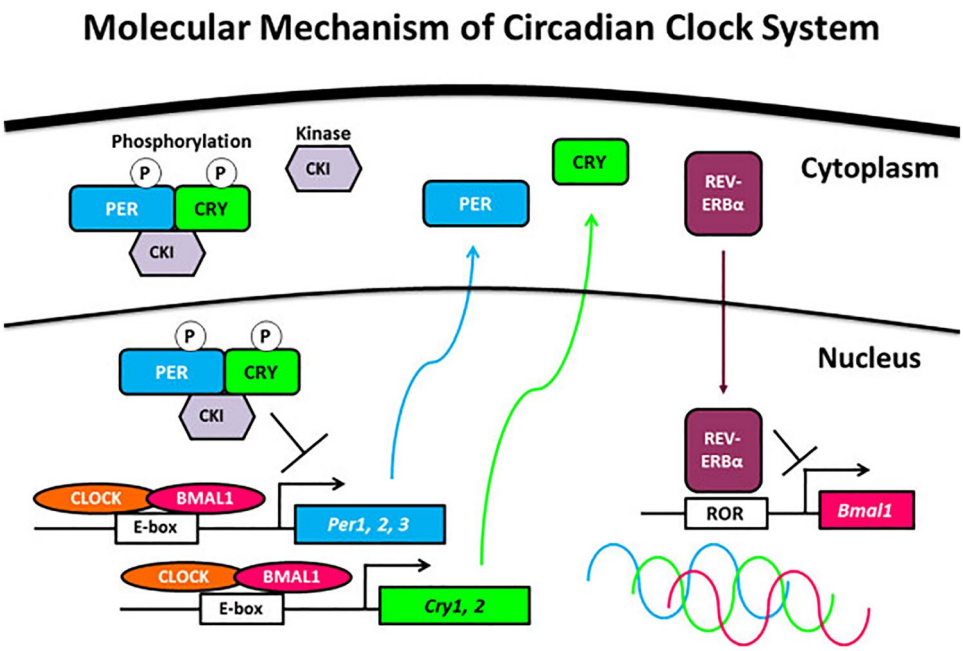


Fig. 2 Schema of the circadian clock system. The foundation of the molecular clock involves a transcription-translation negative feedback loop of clock genes along with post-translational modifications to the genetic products. CLOCK and BMAL1 heterodimerize and promote transcription of Per1-3 and Cry1-2 by binding to E-box elements in promoter regions. Per and Cry gradually build up in the cytoplasm during the biological day. Phosphorylation and binding result in a trimeric complex that can translocate into the nucleus enabling feedback inhibition upon the production of genes promoted by the transcription factors CLOCK and BMAL1 [47]. A second more recently discovered feedback loop is also pictured, which involves nuclear receptors REV-ERBα and a family of retinoid-related orphan receptors (ROR), which primarily regulate BMAL1 transcription and modulate CLOCK expression [45]. Figure reproduced and legend adapted from Hida A, Kitamura S, Mishima K. Pathophysiology and pathogenesis of circadian rhythm sleep disorders. J Physiol Anthropol. 2012; 31(1):7

activated genes are then transcribed, and the protein products are translated and accumulate gradually throughout the biological day, subsequently interacting to form a complex that reenters the nucleus to mediate feedback inhibition by binding to CLOCK and BMAL1, thereby turning off transcription throughout the biological night and directly inhibiting these genes' own production until the proteins degrade as morning comes. In total, the process averages slightly more than 24 h.

Circadian Rhythm Sleep–Wake Disorders

Disorders of the circadian rhythm arise from the endogenous biological rhythm's misalignment with the environmental light-dark cycle. The *International Classification of Sleep Disorders – Third Edition* (*ICSD*-3), developed by the American Academy of Sleep Medicine [51] classifies the circadian rhythm sleep–wake disorders (CRSWDs). Specific requirements for diagnosis of each of the CRSWDs are outlined in the ICSD-3, but in general include a pattern of disruption of the preferred sleep–wake schedule in relation to the observed schedule, for a period of at least 3 months, with resultant adverse consequences, except for jet lag disorder (JLD), which does not include the duration criterion since it may arise on a much more rapid timeframe following transmeridian jet travel [51].

Disruption of the circadian rhythm can originate exogenously or endogenously. These disorders result in nonrestorative sleep, excessive sleepiness, difficulty falling asleep, and/or difficulty maintaining sleep [2]. Two key primary endogenous CRSWDs include delayed sleep–wake phase disorder (DSWPD) and advanced sleep–wake phase disorder (ASWPD). In both cases, the sleep–wake cycle is either delayed or advanced in relation to the desired sleep and wake times. Irregular sleep–wake rhythm disorder (ISWRD) differs, with a chronic, highly chaotic pattern of sleep–wake behaviors. Finally, non-24-h sleep–wake rhythm disorder (Non-24) manifests as a daily drift of the sleep–wake period (as an expression of non-entrained tau) to increasingly delayed (and, less commonly, increasingly advanced) bed and rise times. Exogenous circadian disorders include shift work (SWD), where the circadian system is misaligned with the desired work schedule, and jet lag disorder (JLD), which is caused by rapid time zone changes and the slow-moving circadian rhythm's adjustment to the new time zone.

In both cases, the biological rhythm is not synchronized with the desired sleep or wake schedule.

Further specific details on each of the CRSWDs are provided in a later section of this article to enhance understanding of the specific treatment approach to each of these disorders.

Diagnostic Tools for Circadian Sleep–Wake Rhythm Disorders

Various clinical and research tools are available for use in diagnosing and analyzing CRSWDs [34], including detailed patient histories, sleep diaries, and questionnaires for subjective investigation of a patient's current and desired rhythm.

Questionnaires are commonly used to assess sleep–wake preferences and habits in patients with suspected CRSWDs, including the Morningness-Eveningness Questionnaire (MEQ), which correlates with the physiologic circadian marker of core body temperature (CBT) [52]. The goal of the MEQ is to identify the tendencies and preferences of the subject related to sleeping, wakefulness, and timing of preferred sleep and wake habits [53].

Sleep logs or diaries should be kept for a minimum of 7–14 days to document the patient's longitudinal sleep–wake schedule, ideally in combination with wrist actigraphy [51]. An actigraphy sensor combines an accelerometer and clock to objectively quantify body movements, therefore serving as a surrogate measure of the sleep–wake cycle [54, 55]. Examples of actigraphy monitoring tracings demonstrating normal sleep profiles are shown in Fig. 3.

Estimating the time of melatonin secretion onset can help assess circadian phase and inform timing of treatments for circadian-based interventions, in accordance with the melatonin phase response curve (PRC). There are commercially available dim light melatonin onset (DLMO) kits to quantify DLMO using salivary or urinary samples that can sequentially measure the secretion of melatonin for specified periods during the day and night. Application of the PRCs toward informing timing for light and melatonin therapies is outlined further in the following section on management of the CRSWDs.

Additionally, ambulatory light monitoring (ALM) can measure fluctuations in light exposure throughout the day-night period, providing an objective tool to assess the light-dark cycle directly. However, due to the logistical difficulty of employing these tools and the variability of influences of zeitgebers in real-world settings outside of circadian laboratories, these measures are primarily currently being used in research settings, and require additional validation for clinical use.

Sleep testing such as polysomnography (PSG), multiple sleep latency testing (MSLT), or home sleep apnea testing (HSAT) can also be utilized depending on a patient's individual presentation and the likelihood of other comorbid sleep disorders. Further application of these other sleep studies and their roles are discussed in the articles on sleep-disordered breathing, narcolepsy, and the hypersomnias in this issue of Neurotherapeutics.

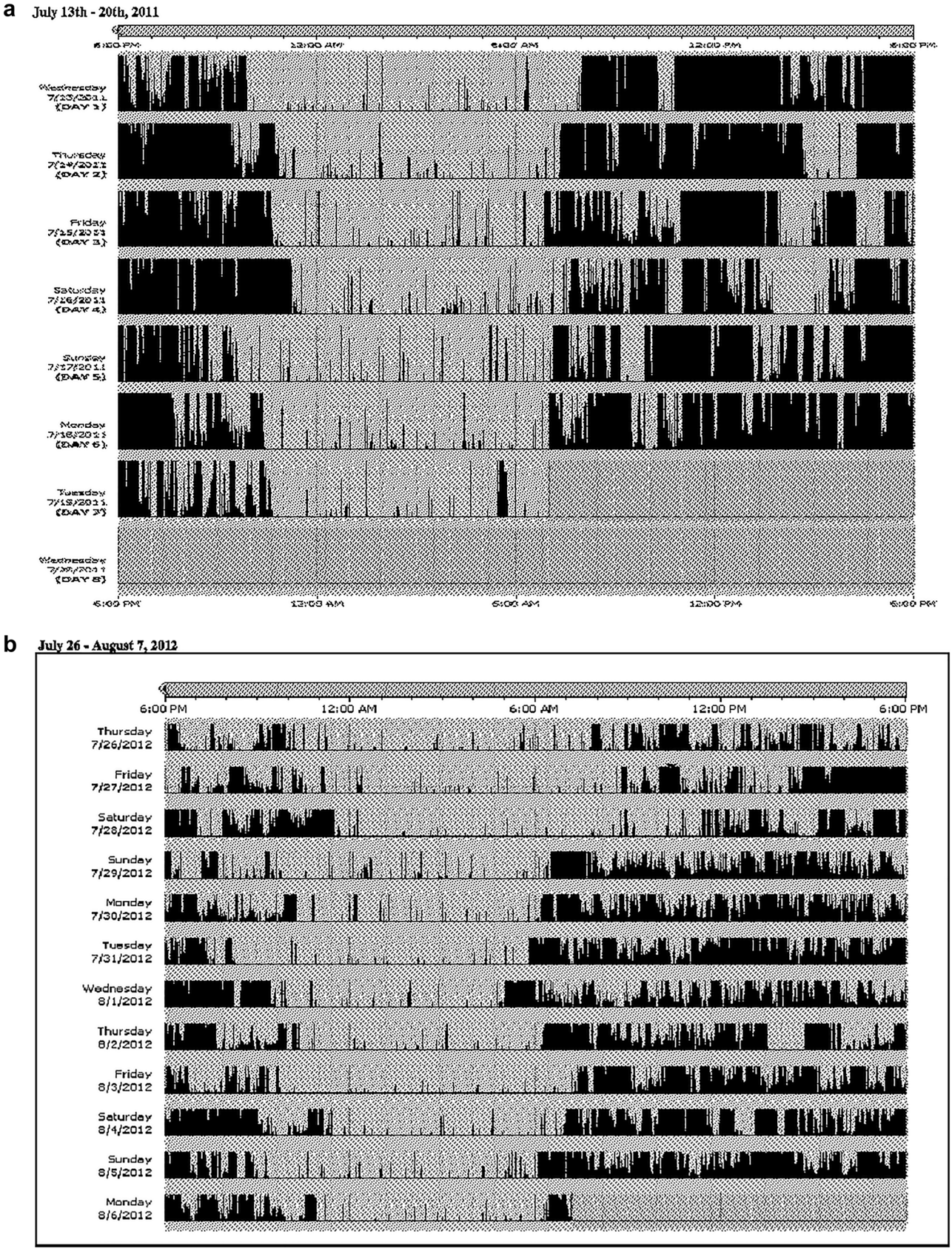
Once a patient with a CRSWD has been accurately diagnosed, the primary focus of treatment is to align the circadian system to their desired schedule. Management options for CRSWDs include strategically timed and administered light, melatonin, prescription pharmacotherapy, behavioral therapies, and/or chronotherapy [2]. Success of the treatments depends on a wide variety of factors, including the timing of treatment administration relative to biological processes in the daily cycle [56, 57]. Management options are now discussed in further detail, as applied for each, of the most common CRSWDs.

Therapeutic Management Strategies for the Circadian Sleep–Wake Rhythm Disorders

The goal of treatment with CRSWDs is to harmonize the endogenous biological clock with the exogenous environment. The precise treatment strategy will vary depending on the desired schedule. The timing of administration of light therapy and melatonin is crucial, although an evidence basis for the optimal timing and dosage within a defined window remains limited [2]. Moreover, maximal circadian changes do not always correlate with optimal clinical effects [58–66].

Both light and melatonin exert their effects according to characteristic phase response curves (PRCs) which determine the phase advancing or delaying direction, as well as the magnitude of their influence on an individual's circadian rhythm. So, depending on their timeframe of administration, these chronotherapeutic therapies may either have a phase advance, a phase delay, or a nil influence [67]. The phase response curve of melatonin is near 180° out of phase with that of the light phase response curve [68].

The PRC revolves around specific anchors that have characteristic timeframes of occurrence: the core body temperature nadir (usually anchored around 5–6 h after habitual sleep onset) and dim light melatonin onset (DLMO, which typically occurs about 2 h prior to habitual sleep onset time). Fig. 4 depicts the light and melatonin PRCs and the opposing phase advancing or delaying effects they exert relative to their time of application [69]. In most cases, bright light therapy given in the morning will phase advance, but if given in the evening/early morning hours prior to CBT minimum, a phase delaying effect will ensue. Conversely,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◂**Fig. 3** Normal actigraphy monitoring profiles, shown for **a** 1-week and **b** 2-week recording periods. Note that in each example, the major sleep period shows a relative paucity of movement activity, whereas during the normal daytime waking period, varying but relatively active movement is seen. **a** Normal actigraphy recording (1 week). The total estimated sleep time in this patient was an average of 7 h 42 min, with sleep efficiency estimated at approximately 94%. The usual sleep period varied from an approximate bedtime between 21:30 and 23:00, while average rise time varied from about 06:00 to 08:00. **b** Normal actigraphy recording (2 weeks). The total estimated sleep time in this patient was an average of 7 h 54 min, with sleep efficiency estimated at approximately 93%. The usual sleep period varied from an approximate bedtime between 22:00 and 23:30, while average rise time varied from about 06:30 to 08:00

melatonin administration in the late afternoon or evening will have a phase advancing effect, while melatonin given after DLMO or in the morning will cause phase delays. Further details on the phase effects of melatonin and light therapy are outlined below.

Melatonin has an array of physiological effects, and its primary role is to signal and inform the brain and body of the darkness segment of the light-dark cycle and thereby also help entrain the SCN to the environment. Oral melatonin can advance or delay the phase of the circadian rhythm depending on the timing of its administration relative to the position of the biological clock [61, 70]. Phase advance occurs when melatonin is given 2 to 7 h before DLMO [61], which typically occurs approximately 2 h before the onset of sleep [68]. A phase delay occurs when melatonin is given in the early morning hours (biological morning) [71]. The oral administration of 0.1–0.3 mg of melatonin results in physiologic plasma levels of 100–200 pg/ml, with a peak at 45 min. Relatively low doses of oral melatonin (0.5 mg) appear to be most effective for phase advancing effects [61]. Since the FDA considers melatonin a dietary supplement, it is affordable and easy to access in the USA, whereas in Europe, there is a marketed and regulated approved formulation, Circadin. To ensure quality, in the USA, melatonin formulations should be US Pharmacopeia verified (USP Verified) [2]. The amount of melatonin contained in various commercially marketed preparations is highly variable [52].

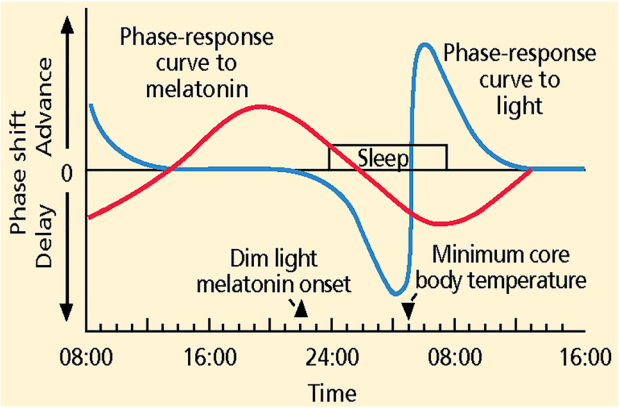

Fig. 4 A schematic human phase-response curve to light (blue line) and to exogenous melatonin (red line). The *y* axis shows the direction and relative magnitude of the phase shift produced by the administration of light or melatonin at various times, which are shown on the *x* axis. This graph shows typical times and phase relationships among these rhythms when the circadian clock is entrained to a 24-h day. For individuals with earlier or later circadian rhythms, the local time axis should be adjusted accordingly. The light phase-response curve is a schematic based on the results of numerous studies. The melatonin curve is based on a single study using 0.5-mg doses of melatonin. Used with permission from Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. Sleep Med Rev. 2002;6(5):407-20

Light therapy is another fundamental chronotherapeutic for CRSWDs. Light administration prevents melatonin release by inhibiting the SCN's activation of the pineal gland. With proper wavelength, duration, and intensity, the circadian rhythm can be phase shifted, with varying effects depending on the prescribed time of administration and exposure. When a person is normally entrained and light is administered before the CBT minimum (for practical purposes, during evening hours), it will have a phase delaying effect. By contrast, when light is administered after CBT minimum (in the early hours of the morning), it will have a phase advancing effect [72]. Typically, light therapy should be administered for a minimum of 30 min, although ideal duration, dosage, and luminance still remain to be determined [73–75]. Although light therapy is usually well-tolerated, extra care should be taken when patients are also receiving photosensitizing medications. Headaches and eye strain are the most common side effects of light therapy [73, 76]. Some data suggest combined light and melatonin administration may be advantageous because a greater magnitude of phase advance has been seen using combination therapy than with light or melatonin individually [77]. Adjunctive hypnotic or stimulant medications can sometimes aid the treatment process in selected patients, although little evidence exists for use of these approaches in the setting of CRSWDs [2].

Additionally, minimizing evening light exposure may be helpful to avoid exacerbating or causing phase delays in bedtime and the sleep cycle. Behavioral avoidance of bright light sources such as computers, video games, cell phones, iPads, or other personal devices can be recommended as a reasonable and biologically rational strategic approach toward the prevention and management of delayed sleep–wake phase disorder (DSWPD) in particular, but as yet, little evidence is available to guide specific recommendations on the timing and duration of light restriction, or which specific wavelengths/luminances are to be avoided. Commercially available blue light blocking glasses can be recommended for use in the evenings in patients with DSWPD, but these await further evidence basis for their

more widespread adoption and specific recommendations on their use [78].

Behavioral modifications may also be helpful, such as healthy lifestyle and traditional sleep behavior tips, for example, maintaining a regular sleep schedule, keeping the bedroom cool, dark, and quiet, and avoiding caffeine and alcohol. Chronotherapy, a rapidly progressive phase delay in the patient's bed and rise times by 3–4-h intervals every other day, can also be considered, but this strategy is difficult to operationalize, and controlled studies establishing its efficacy, tolerability, and safety are lacking [73, 81] [71, 79].

Specific Circadian Rhythm Sleep–Wake Disorders and Their Chronotherapeutic Management Strategies

Jet Lag Disorder

In the modern world of transoceanic commuting, people often experience the effects of jet lag disorder (JLD). JLD is simply a misalignment of the internal biological clock (which remains temporarily entrained to the patient's own typical home time zone) with the new exogenous time zone following rapid transmeridian travel. Typically, depending on the individual's phase tolerance, adapting to the new local time zone may take around one day per time zone shift [80]. The goal of treatment is generally to delay (for westward travel) or to advance (for eastward travel) the innate timing of the sleep–wake schedule, with estimated CBT minimum serving as the typical target of interest. Since this nadir occurs approximately 3 h before waking in the entrained setting, circadian-based interventions aim to establish the same relationship in the destination time zone [81].

For instance, travelling eastward from Los Angeles to New York involves a 3-h time zone shift. This means that on arrival in the new Eastern Standard Time (EST) zone, for an individual who was previously entrained to Pacific Standard Time (PST) on the West Coast, the traveler's CBT minimum will be roughly 3 h behind, so falling asleep readily in the new EST zone is difficult. If the CBT minimum was normally 3:00 when entrained to PST, CBT minimum will become 6:00 the first night/day in New York. By avoiding light for 3 h prior to the new CBT minimum (beginning at 6:00) and seeking light (ambient or medical grade light box) for the same duration beginning at 09:00 (3 h after the CBT minimum), the phase can be advanced. The process is repeated on a daily basis, assuming 1.5-h phase advancements (1.5-h earlier timing of the CBT), until it is estimated to lie within 1 h of the desired time in the destination time zone (If the individual hoped to observe the same sleep–wake schedule as home, destination CBT minimum would occur near 3:00).

If the direction of travel was instead westward from New York to Los Angeles, the patient's native EST circadian rhythm will need to phase delay to entrain to the destination PST [81]. This is accomplished by seeking light (ambient or medical grade light box) 3 h prior to estimated CBT minimum and avoiding light exposure for the 3 h following CBT minimum. The process is repeated on a daily basis, assuming 2-h phase delays (2 h later timing of the CBT), until it is estimated to lie within 1 h of the desired time in the destination time zone (If the individual hoped to observe the same sleep–wake schedule as home, destination CBT minimum would occur near 3:00 in the new local time zone, PST).

In addition, melatonin can be used to aid in entrainment. One strategy suggests evening melatonin therapy dosed at 2 mg or 5 mg upon arrival at the destination bedtime for 4–5 days [82–84], or some studies have recommended a more complex regimen initiating melatonin therapy 5 mg in the native time zone at the corresponding destination bedtime for 3 days prior to travel, and continued therapy for 3–4 days in the new time zone [85, 86].

Shift Work Disorder

Another exogenous CRSWD is shift work disorder (SWD). This occurs when the endogenous circadian rhythm is not aligned with the desired sleep–wake schedule. Typically, this includes an assigned work shift during the conventional sleep time, either on a rotating or permanent schedule. A number of industrial accidents (Chernobyl in Pripyat, Ukraine) [87], transportation accidents (Exxon Valdez oil spill near Alaska, USA) [88], and space launch accidents (explosion of Space Shuttle Challenger, Atlantic Ocean) have fatigue or sleepiness related to shift work as one of the contributing factors underlying the accident [87].

Approximately 15% of full-time workers perform shift work in the USA according to the Bureau of Labor Statistics [89], and an even larger number of part-time workers are likely impacted by SWD. This percentage varies internationally [90]. Almost 17% of men perform shift work, compared to 12.4% of women. White Americans are less likely (13.7%) to perform shift work than African Americans (20.8%), Asian Americans (15.7%), and those of Hispanic or Latino ethnicity (16.0%). Shift work is most commonly seen in service occupations (32.6%), such as healthcare, protective services, and maintenance occupations, and production/transportation occupations (26.2%) [89].

As a population, shift workers have been documented to have decreased total sleep time (TST) [91, 92]. For those with actual SWD, common symptoms include excessive sleepiness during the work period and insomnia when attempting to sleep during the day. These symptoms and

sleep loss may lead to increased work-related errors [93], fatigue [94], and depressive and anxiety symptoms [95]. Shift work has also been shown to lead to a broad array of adverse health effects [96].

The *ICSD*-3 criteria for the diagnosis of SWD rely on an in-depth clinical history to ensure another disorder does not better explain the symptoms and distress [51]. The symptoms of insomnia, excessive daytime sleepiness, or both must be present for at least 3 months with associated functional impairment. Additionally, at least 14 days of actigraphy is required, ideally including both work and non-work days, along with a sleep diary [51].

The goal of treatment for SWD disorder may vary depending on the timing of the work schedule, non-work-related commitments (e.g., family, social), or frequency of rotation. The general intention is to align the endogenous circadian rhythm with the desired sleep–wake schedule. When the diagnosis of SWD is made, cessation of shift work would be the most desirable solution, yet this is not always feasible (e.g., childcare), and other measures may need to be taken. An example of actigraphy monitoring of a patient with SWD is shown in Fig. 5 [97], demonstrating a particularly brittle "swing shift" worker with alternating day-night shifts, and a complete inability (or unwillingness) by her work managers to compromise on her work assignments despite physician advocacy for a switch to steady daytime shift assignments.

Timing of light therapy for SWD varies with the goals of treatment and needs to be individualized for those with rotating schedules or complex social situations. Some studies have investigated unique "compromise phases" to alleviate distressful work-related symptoms while maintaining social responsibilities [98–100]. In addition to circadian rhythm management, medications can be employed to strategically promote sleep or wakefulness. Few studies have targeted

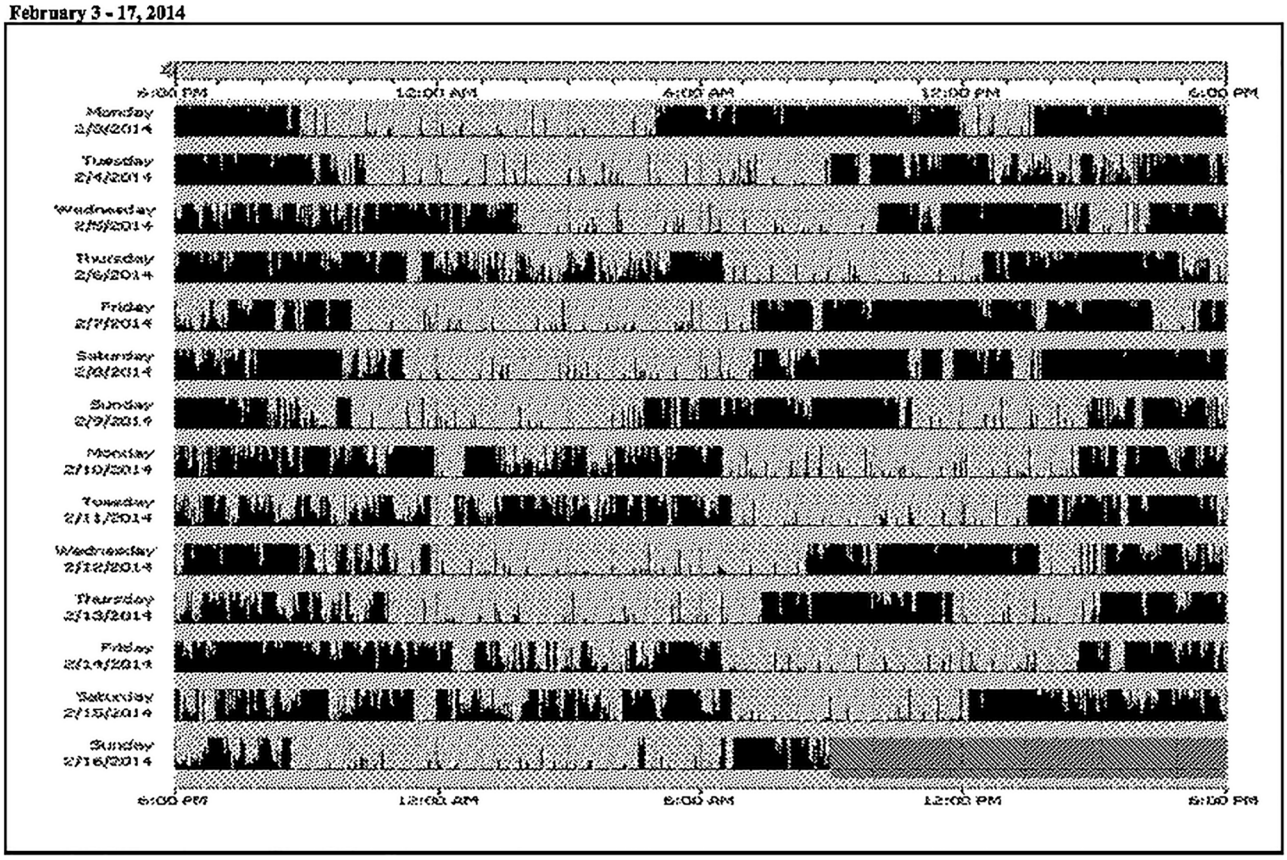

Fig. 5 Actigraphy monitoring in shift work disorder. This 42-year-old woman was employed as a police and fire dispatcher in a rural vicinity, with work shift requirements for alternating "swing" shift work alternating between morning, afternoon, or overnight evening shifts every few days. Her morning daytime shifts were from 07:00 to 12:00, her afternoon shifts typically began at 16:00 and lasted until 23:00, and her overnight evening shifts were scheduled from 22:00 to 06:00. Shifts alternated every 2–3 days throughout the work week, with every other weekend off from work. She was a single mother of an 11-year-old son, requiring her to often have abbreviated or incomplete sleep periods to take care of her son or to drive him to activities when she was off from work. She had profound daytime sleepiness with an Epworth Sleepiness Scale score of 22 (abnormal, > 10 [97]), despite treatment with modafinil 400 mg during periods of wakefulness prior to her commutes to work. The actigraphy findings demonstrate regular well-consolidated sleep–wake periods mirroring her described work shift patterns

symptoms of sleep disturbance in the setting of circadian misalignment. Generally, hypnotic therapy may improve pre-shift sleep quality in order to maintain alertness and performance during the ensuing work shift schedule. Modafinil and armodafinil are both approved by the FDA for excessive sleepiness in SWD. Armodafinil benefits objective sleepiness [101] and performance, as well as post-shift driving safety in those with SWD [102]. Modafinil also showed improvements in driving although subjectively sleepiness was unchanged [103]. Also, a combination of caffeine with strategically timed napping has been shown to improve excessive sleepiness and performance [104].

Delayed Sleep–Wake Phase Disorder

The most common and well-studied endogenous CRSWD is DSWPD, which is characterized by a delayed sleep onset and offset beyond the desired or traditional times. Often referred to as "night owls," DSWPD patients may subjectively describe feelings of optimal performance and alertness in the evening hours. Patients with DSWPD are most often unable to initiate sleep until the early morning hours, typically between 02:00 and 04:00, sleep periods are of fairly normal duration of 7–8 h, followed by preferred awakening time between 10:00 and 13:00. A typical actigraphy recording of a patient with DSWPD is shown in Fig. 6.

When attempting to adapt to a traditional schedule for normal activities involving a morning rise and start time, including school, work, social obligations, and other responsibilities, those suffering from DSWPD are very likely to experience distress and symptoms of dysfunction resulting from their inability to initiate sleep onset at an appropriately earlier desired time (leading to a period of initial insomnia). The following morning, given their habitual preferred later time for sleep offset, when these patients are forced to arise earlier before they have obtained sufficiently restorative sleep, upon awakening, sleep inertia with impaired performance, grogginess, fatigue, and a strong desire to return to sleep usually ensues. In DSWPD, difficulty falling asleep at the desired time and awakening prior to fully restorative

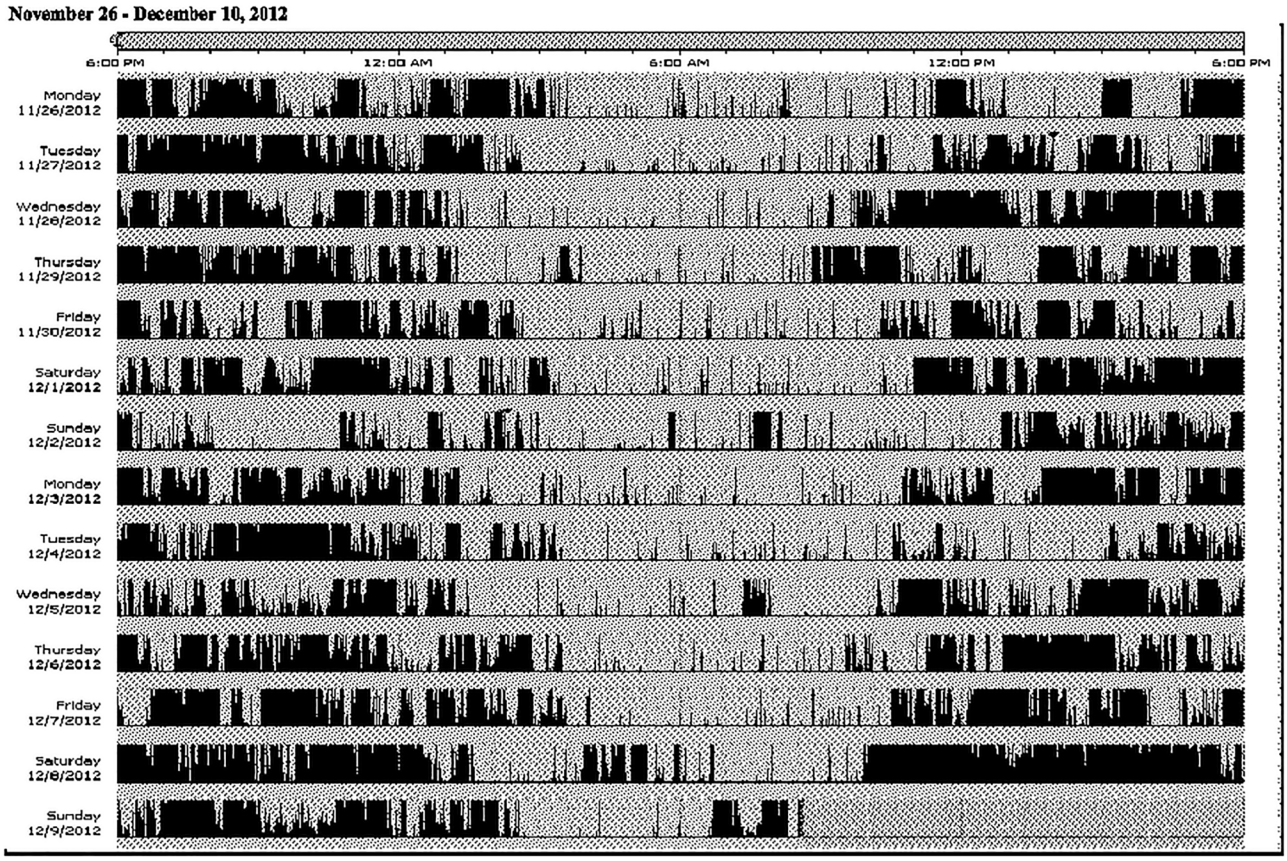

Fig. 6 Actigraphy recording of a 22-year-old man with delayed sleep–wake phase disorder. Average total sleep time estimate was 6 h 34 min. The patient's average bedtime was approximately 02:30, with average rise time of 10:30. There was some additional variability in bed and rise times that also implied inadequate sleep hygiene (irregular sleep habits). Morning bright light therapy and melatonin 0.5 mg at 1800 were prescribed, with subsequent improvement in ability to bed and fall asleep earlier around 00:00 midnight and rise by 07:00 with relief of daytime sleepiness

sleep causes chronic sleep deprivation. Symptoms must be present for at least 3 months by *ICSD*-3 diagnostic standards. Due to often severe initial insomnia symptoms, patients may attempt to use sleep-promoting agents. If allowed to sleep and wake on the patient's desired delayed sleep onset and offset schedule, a resumption of normal sleep duration and quality with a cessation of distressing symptoms will occur. For some people with DSWPD, choice of an occupation that enables them to embrace their preferred delayed sleep schedule (i.e., for some musicians, artists, or second/third shift workers), this adaptive lifestyle may lead to complete resolution of symptoms.

DSWPD is most common in young adults and adolescents. A maximal preference towards a delayed sleep–wake phase is evident at approximately 20 years of age, and advanced phase becomes increasingly favored beyond this point [105]. The epidemiology of DSPWD is difficult to identify and can differ widely internationally due to varying cultural obligations, workplace habits, and school start times [79].

Diagnosing DSWPD may be challenging due to the patient's self-management strategies and comorbidities. Oftentimes, there is comorbid insomnia, depression [106], anxiety [107], and other psychiatric conditions, and there appears to be a bidirectional relationship between mental health and "eveningness" [108], with some evidence from animal models and humans that "eveningness" and phase delay may be an endophenotypic or even prodromal marker for mood disorders [109]. At least 7 days of actigraphy monitoring and/or sleep diaries are necessary to diagnose DSWPD.

Treatments of DSWPD involve manipulating the circadian rhythm to align with the desired school or work schedule and subsequently anchoring the desired schedule to maintain it. Light therapy and melatonin are the mainstays, but few rigorous, large-scale, randomized studies target DSWPD. Phase advancement of the circadian rhythm can be achieved by light therapy administered upon awakening and low-dose melatonin administered in the evening about 5 h before DLMO [110, 111]. Hypnotics and stimulants have not been systematically studied in DSWPD but can provide benefit to carefully selected individual patients to aid their functioning and wellbeing [2]. Evening light restriction, especially in the 2-h timeframe before bedtime, should be recommended, with limitation of screen time on computers, cell phones, IPads, or other devices with sources of luminance in the evening hours in the hours prior to bedtime, and use of commercial blue light blocking glasses in the evening can also be considered (although further evidence on the efficacy of these sensible yet thus far unestablished interventions in DSWPD management is needed).

Cognitive behavioral therapy for insomnia coupled with light therapy may be useful in DSWPD and have a long-lasting positive impact [64]. It has also been shown to significantly reduce depression and anxiety symptoms and significantly decrease the Insomnia Severity Index [65].

Additional randomized trials for the best management strategies of DSWPD are needed. Since most patients with DSWPD are young adults and adolescents, targeted, community-based interventions for later school start times have led to improvements in student wellbeing, TST, decreased tardiness, and academic performance [112–114].

Advanced Sleep–Wake Phase Disorder

In ASWPD, there is an undesirable advance in both sleep onset and offset, a condition often referred to as being a "morning lark." In the case of ASWPD, the patient becomes sleepy earlier than desired in the evening (often as early as 18:00–21:00) and awakens too early in the morning (usually between 2:00 and 5:00). As with DSWPD, the endogenous circadian rhythm remains properly entrained to the 24-h light-dark cycle but is shifted earlier in time from the desired or required sleep–wake schedule.

DSWPD may culturally (although inappropriately) be considered a form of "laziness" because a patient prefers a delayed schedule with late morning awakenings. However, the traits of advanced sleep phase are more often viewed positively. The early bird mentality may be more socially accepted, which may cause the patient and their families to fail to recognize this disorder, thereby delaying a patient seeking clinical assessment.

Given these challenges, the epidemiology of ASWPD has been difficult to determine. Most estimates have shown an approximate 1% prevalence for ASWPD, depending on the specific criteria used [115, 116]. Interestingly, one Norwegian study found no cases among a cohort of 7700 people [117]. ASWPD occurs more often in the older population and impacts more men than women [118, 119]. Some evidence indicates premature children are more susceptible to ASWPD [120].

Like DSWPD, the diagnosis of ASWPD requires a thorough clinical history, and questionnaires such as the Horne Ostberg Morningness-Evenginess Questionnaire (MEQ) [121, 122] can be used to identify personal circadian preferences and chronotype. To confirm the clinical history, objective tracking of the sleep–wake schedule with a minimum of 7-day collection of sleep diary and/or wrist actigraphy monitoring is necessary. See Fig. 7 for an example of an elderly man with ASWPD. The disorder must also persist for at least 3 months and should not be better explained by other disorders; as in DSWPD, a bidirectional relationship with mental health is apparent in individuals with "morningness," sometimes presenting an additional challenge to accurate diagnosis and requiring further study [108]. Importantly, if allowed to resume the habitual sleep and wake schedule,

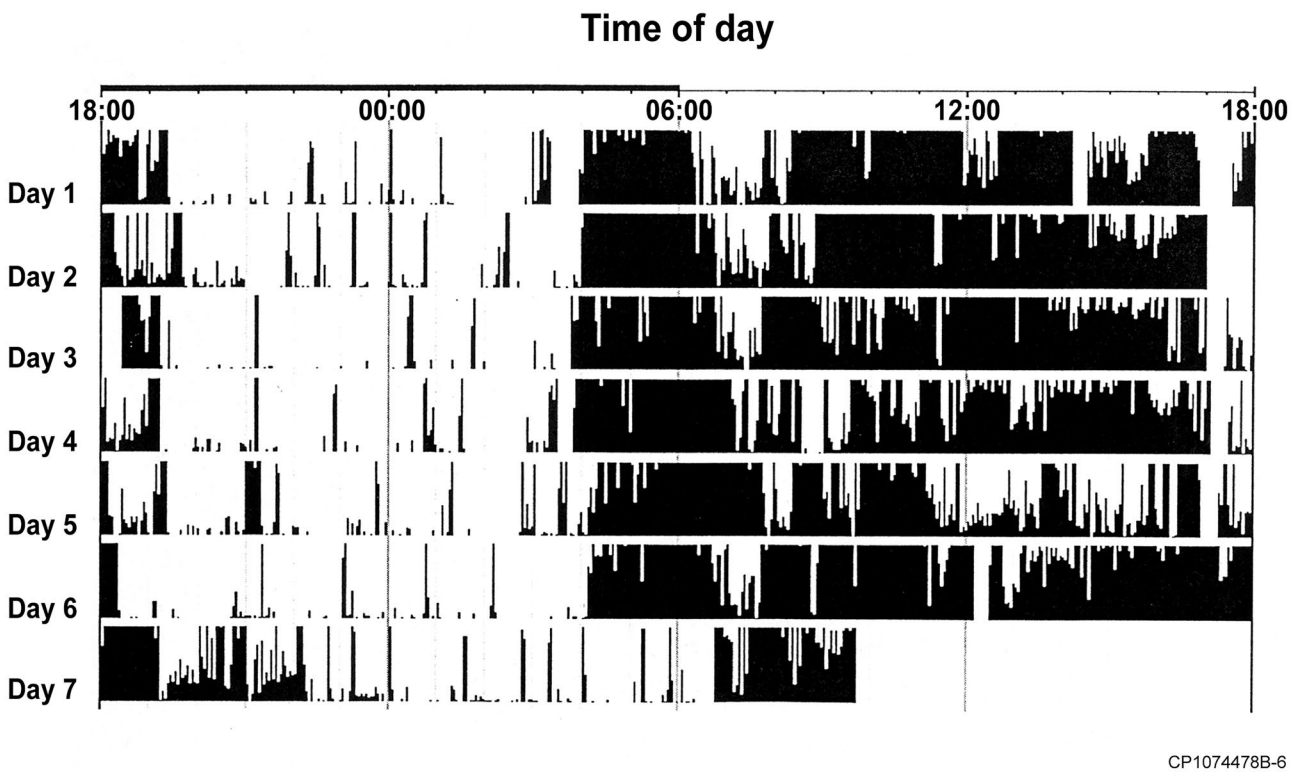

Fig 7. Wrist actigraphy documentation of advanced sleep–wake phase disorder in a 73-year-old man. Note the average sleep onset time with an average of approximately 1900 h, with early rise time near average of 0400

the symptoms of evening hypersomnolence and maintenance insomnia will subside.

Treatment of ASWPD involves realigning the endogenous circadian rhythm with the desired sleep–wake schedule. Clinical trials targeting ASWPD remain limited. As with DSWPD, the phase response curve can be manipulated by strategic application of timed light and melatonin therapies to delay the circadian rhythm. Light administered between 20:00 and 23:00 h was shown in one pivotal study to delay the phase as measured by CBT, although only variable efficacy or negative outcomes has been seen in other studies given variability in light dosing, adherence, and definitions used for ASWPD [123–128]. Evening light application, especially in the 2-h timeframe before bedtime, should be recommended.

Administering exogenous melatonin during the biological morning may also influence the phase response curve by inducing phase delays. This remains unproven in clinical settings to date, and a precaution is to forewarn patients of possible adverse hypnotic effects induced by daytime administration of melatonin. In addition to light and melatonin, hypnotics and stimulants can also be used with caution for symptomatic treatment. Behavioral therapy applicable in ASWPD may include advising avoidance of early evening naps, since the largest magnitude of phase advance in daytime napping is seen in the evening at an average of 44 min [129].

Non-24-h Sleep–Wake Rhythm Disorder

Non-24, also referred to as Free-Running Disorder, is a unique endogenous CRSWD. As previously mentioned, the average human circadian rhythm period (tau) is slightly longer than a day at approximately 24.18 h [8]. If allowed to remain in constant (non-entrained) conditions, in a cave or an underground bunker for example, the circadian rhythm will persist, but the period will be slightly longer than a day and will eventually fall out of sync with the light and dark cycle. However, in Non-24 disorder, the individual's own unique tau period is either markedly shorter or, more commonly, markedly longer in duration than 24 h, and even with cues of entrainment, the Non-24 patient's tau does not properly adjust to the exogenous environment. This causes a daily drift where, depending on the duration of the patient's individual tau, the direction of sleep onset and offset will progressively shift in time. If the circadian rhythm period is longer than average (e.g., 25 h), each day the sleep offset and onset time will shift an hour later.

Since the primary zeitgeber is light, the inability to receive photic input, possibly through nonfunctioning

ipRGCs or the RHT, makes alignment of the endogenous rhythm to the exogenous clock difficult. Current estimates suggest as many as 70% of non-sighted individuals lack light perception and/or may lack exposure to light or nonphotic zeitgebers, such as physical activity, and may therefore be vulnerable to develop Non-24 [130, 131]. The epidemiology of Non-24 has been difficult to establish due to the rarity of the disorder, but it seems to be more common among non-sighted individuals, although case reports have also documented Non-24 in sighted individuals.

The diagnosis of Non-24 can be challenging because its presentation may vary as the patient's endogenous tau progresses through the exogenous clock time of day/night, with varying presentations that result in either insomnia or hypersomnia. A detailed clinical history is important because patients may or may not be aware of this pattern themselves. The disorder must be present for at least 3 months. Due to the unique nature of Non-24, there must be 14 days, at minimum, of actigraphy and/or sleep logs to accurately characterize and substantiate the progressive drift of tau and to estimate the period length [51]. Fig. 8 shows an example of actigraphy monitoring in a 24-year-old non-sighted man with Non-24.

The goal of treatment for Non-24 is to align the endogenous biological clock with the exogenous light and dark cycle of 24 h. Successful treatment will realign the circadian rhythm, anchor the timing in that location, and prevent further daily drift. In the previous disorders, light was discussed as the primary zeitgeber and most powerful tool to aid entrainment. In Non-24, clinicians may encounter individuals who cannot be entrained by light therapy. This presents a unique challenge to a subset of patients with the disorder.

A number of studies have been conducted in non-sighted individuals with timed administration of melatonin to entrain the circadian rhythm [132–136]. Melatonin at doses of 0.5 mg or 10 mg at 21:00 or 1 h before bedtime for 4 to 12 weeks led to the entrainment of 67% of non-sighted individuals with Non-24 [2]. Only small open-label studies and case reports have been published on the treatment of sighted individuals with Non-24 [137–141] including a case treated with the melatonin agonist ramelteon [142].

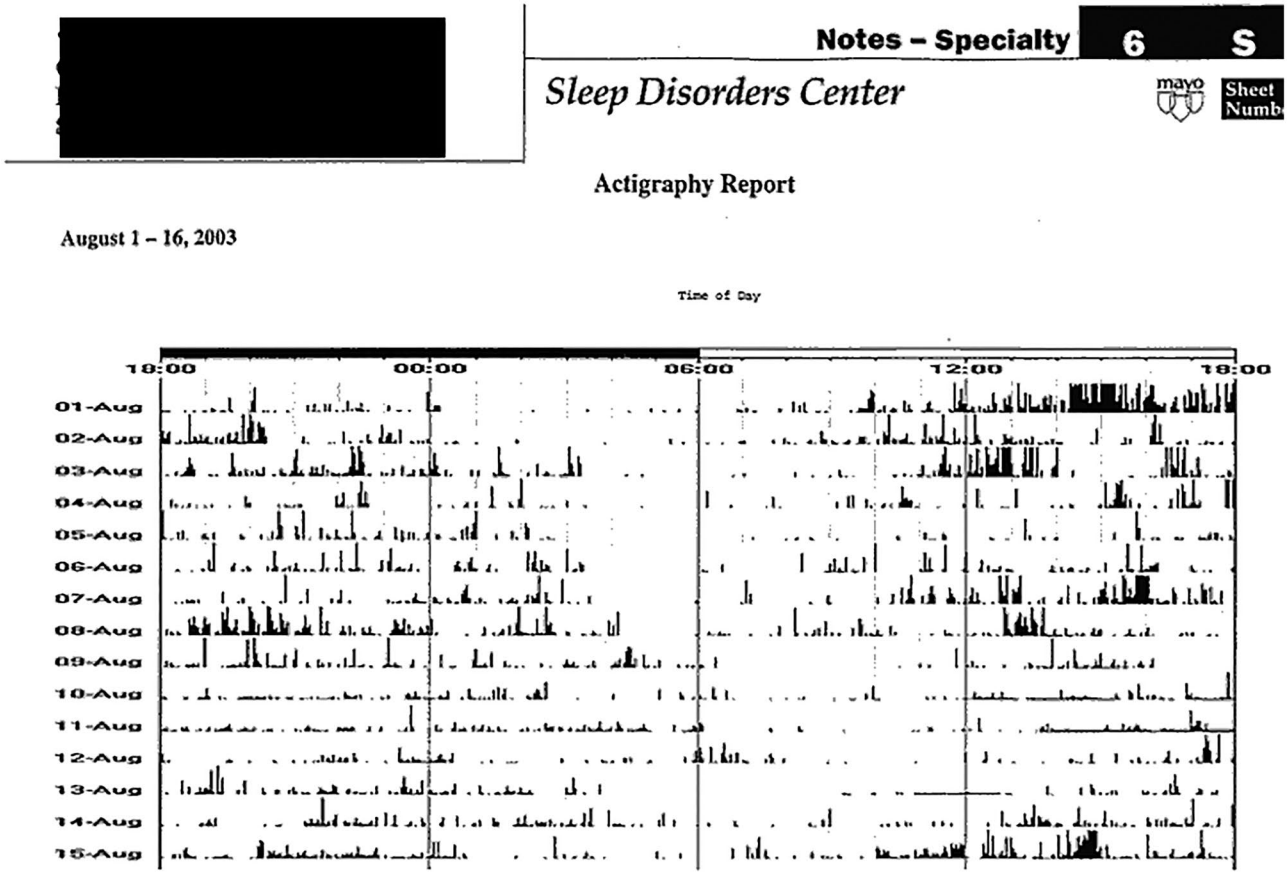

Fig 8. Wrist actigraphy monitoring in a 24-year-old non-sighted man confirmatory of non-24-h sleep–wake rhythm disorder. Note the progressively delayed sleep-onset times in successive nights, suggestive of an endogenous prolonged tau period of longer than 24 h causing successive delays in sleep onset and subsequent sleep periods and rise times

In 2014, tasimelteon became the first FDA-approved treatment for any CRSWD when it was approved for the treatment of Non-24. In clinical trials, tasimelteon has been shown to be superior to placebo for initial entrainment of the circadian rhythm when dosed at 20 mg 1 h before bedtime for 4 weeks, but its entrainment effects were more robust at 50% following 12–18 weeks of treatment, and up to 59% of patients entrained following 7 months [131]. Additional sleep benefits include shorter initial sleep latency and improved sleep maintenance [143]. Tasimelteon is typically well-tolerated, and the most commonly reported adverse effect is headache [131], while abnormal dream mentation, nausea, urinary and upper respiratory infections, and elevated alanine aminotransferase have also been reported [144]. Tasimelteon is a melatonin receptor agonist of MT1 and MT2 receptors, with a higher affinity for MT2, thought to be the key receptor involved in phase shifting the biological circadian clock [145].

Irregular Sleep–Wake Rhythm Disorder

ISWRD involves highly irregular sleep–wake cycles with sleep and wake times seemingly random in duration and highly chaotic throughout the 24-h period, without a discernable circadian pattern or rhythm. The cycles are short and unpredictable and can occur multiple times within a 24-h period (see Fig. 9). The bouts of sleep are not aligned with any particular exogenous zeitgeber or influence, and sleep often occurs during undesirable daytime periods. This disorder is usually severe and causes significant difficulties in daily life for both patients and their caregivers.

Healthy individuals may present with ISWRD as a result of extremely poor sleep hygiene. However, ISWRD is most common among those with underlying injury or destruction of the hypothalamic SCN or its inputs or outputs, mediated by neurodegenerative disease, neurodevelopmental disorders, or traumatic brain injury (TBI) [146]. Post-mortem

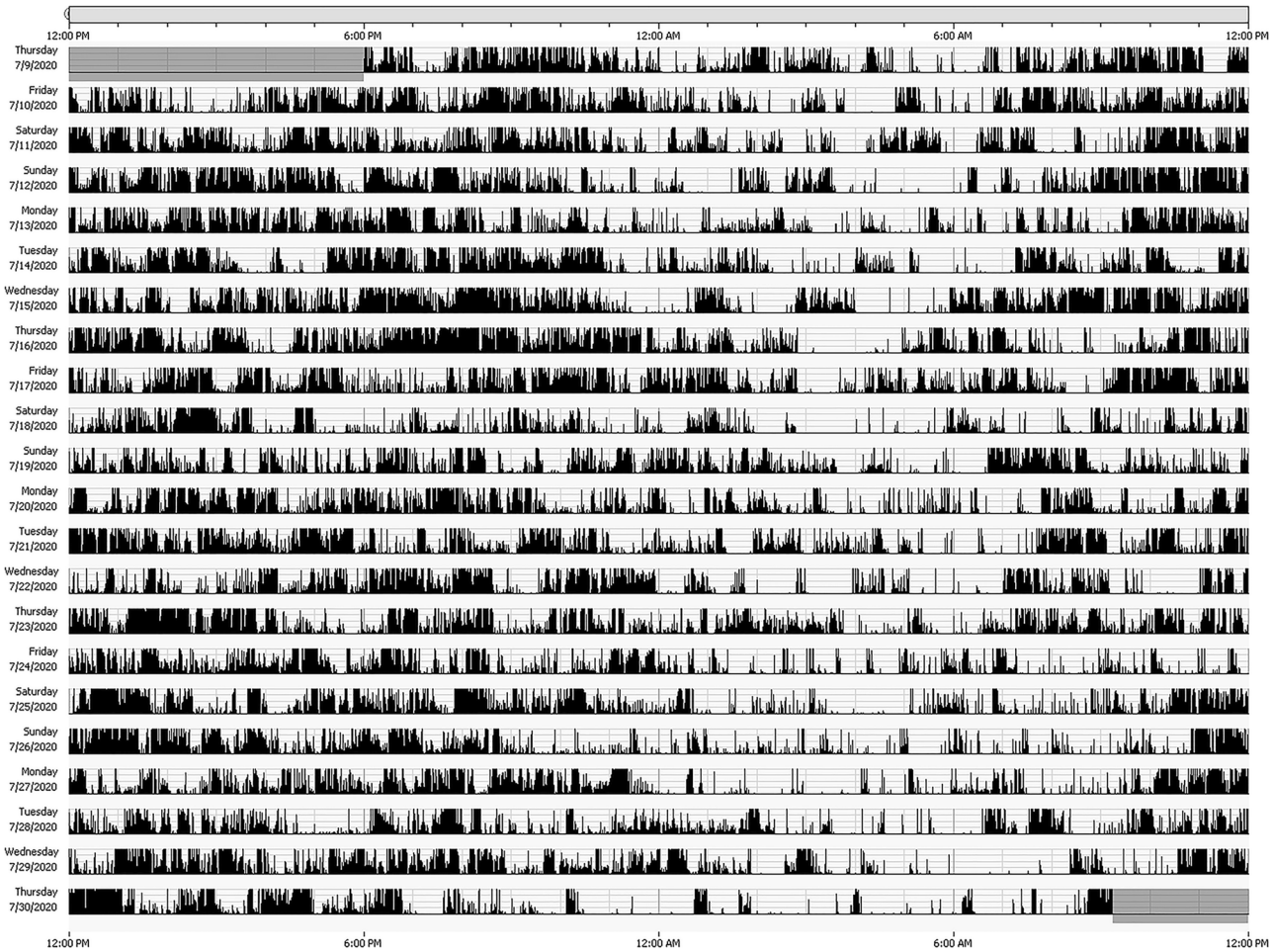

Fig. 9 Actigraphy recording for 3 weeks in a patient with ISWRD. Note the highly chaotic, irregular, and disorganized brief bouts of activity alternating with inactivity (likely sleep) seen throughout the daytime and nighttime, without an obvious sustained sleep or wake period. There are rarely more than 1 to 3 h of consolidated sleep or more than 1–2 h of wake time

examinations of patients with ISWRD have confirmed hypothalamic pathology. In patients with Alzheimer's disease, degeneration and neurofibrillary tangles in the SCN [147] and disruption of the ipRGCs have been reported [148]. Additionally, as people age, nighttime melatonin secretion decreases, which has significant implications for the robustness of the circadian rhythm. In aged, institutionalized populations, irregular light exposure and alterations in social interactions are also likely contributions to a more irregular sleep–wake pattern.

The epidemiology of ISWRD remains undefined, likely due to difficulties in accurate diagnosis of ISWRD. Common symptoms include excessive daytime sleepiness, insomnia, or both. As the cognitive functioning and independence of the patient declines, collateral history from caregiver reports may become necessary. In addition to the clinical history, 7–14 days of actigraphy and/or sleep logs are necessary to confirm the irregular schedule (see Fig. 9). The overall symptoms must be present for at least 3 months [51].

Treatment for ISWRD is challenging, and outcomes often depend on the underlying neurodegenerative or neurodevelopmental etiology [146]. Successful treatment of ISWRD depends on individual limitations and pathophysiology, with a basic goal of restoring a more consolidated sleep–wake pattern and decreasing fragmentation of the sleep–wake cycle. A good starting point is to assess the current exogenous circadian cues. More robust regulation of the light cycle, physical and social activity, and mealtimes should be optimized as possible to assist in entrainment [149].

Different treatment approaches and regimens have been used in different patient subpopulations. For institutionalized elderly patients with a neurodegenerative disease, the American Academy of Sleep Medicine recommends melatonin and hypnotics be avoided due to the possibility of adverse effects such as deteriorating cognition and falls along with an overall lack of proven efficacy in this subpopulation [2]. Conversely, evening melatonin at doses of 2 to 6 mg may be considered in children and adolescents with neurodevelopmental disorders, especially autism spectrum disorders with severely disturbed sleep–wake patterns, although caution must be taken to monitor for severe daytime sedation, which may occur in patients having a SNP of CYP1A2, leading to slow metabolism of melatonin [2, 150, 151].

Circadian Disruption, Chronotherapies, and Neurodegeneration

Disturbances of sleep and alertness are common in neurodegenerative disorders such as Alzheimer, Parkinson, and Huntington diseases. Sleep dysfunctions may predate the development of neurodegenerative disorders by years, even decades. For example, REM sleep behavior disorder represents the most significant prodromal manifestation of a synuclein-specific neurodegenerative disorder, and excessive daytime sleepiness has been associated with the development of Parkinson disease (PD) [152, 153]. Disruption of circadian homeostasis has been increasingly recognized as an important mechanism underlying disruption of sleep–wake cycles and possibly other manifestations of these disorders [154].

Parkinson's Disease

Alterations in circadian function in PD have been recognized at the behavioral, physiological, and molecular levels, both within the PD population and in the experimental models of the disease. Progressive deterioration of sleep–wake cycles with dramatic reductions in the amplitude of the rest-activity rhythms have been well demonstrated in individuals with PD [155]. In a recent study of 2930 community-dwelling men enrolled in the Osteoporotic Fracture in Men Study, decreased circadian amplitude, mesor, or robustness at baseline were strongly associated with a higher risk of developing PD within an 11-year follow-up [156]. These findings position circadian disruption as a risk factor for PD and suggest a bi-directional relationship between PD and circadian regulation. Pre-existing circadian disruption potentiates the effects of subsequently induced Parkinsonism on dopaminergic cell loss and inflammatory response in experimental models of PD, suggesting circadian dysregulation as an environmental risk factor for PD [157]. In addition to sleep fragmentation and excessive sleepiness, several other physiological rhythms have altered circadian profiles in PD. Examples include reduced amplitude of melatonin secretion [158, 159], reversal of physiologic rhythm of blood pressure and heart rate [160], and changes in ocular contrast sensitivity [161]. Changes in circadian expression of core CLOCK genes have also been reported, with BMAL1 oscillations being most affected [158].

Changes in circadian regulation in PD reported to date provide the basis for exploring circadian-based interventions as a management strategy for PD. Further, the possibility that circadian disruption potentiates the effects of PD-specific neurodegenerative processes opens up a window of opportunity to explore circadian approaches for disease modification. Light is the most potent zeitgeber of the human circadian system and, as such, plays a critical role in the regulation of behavioral and physiological functions. In the PD population, several studies so far have assessed the safety and therapeutic efficacy of light therapy [162]. In these studies, participants with PD were exposed to active and sham light therapy once to twice daily, for 0.5–1.5 h of light pulses of 300–10,000 lx in intensity during 1 to 5 weeks. These studies revealed significant improvement of motor function including bradykinesia, tremor, rigidity, nocturnal

movement, dyskinesia, and balance. The improved non-motor symptoms included insomnia, anxiety, and depression. Light therapy was well-tolerated, and its effectiveness was dependent on the patients' compliance. These promising results support the need for future research that will further refine light therapy protocols in PD. Melatonin has a critical role in synchronization of circadian rhythms. Within the PD population, melatonin demonstrated beneficial effects on the subjective quality of sleep [163]. However, these investigations examined the soporific action of melatonin rather than its effects as a modulator of the circadian system and the AASM's cautionary measures should be considered. The effects of melatonin as a circadian synchronizer await future study. Physical activity and exercise are important non-photic zeitgebers for the circadian system, and exercise trials have shown improvements in PD patients in their off-state motor dysfunction, mobility [164–166], walking performance, co-morbid and anxiety and depressive symptoms, cardiorespiratory fitness, and in spiritual wellbeing and health-related quality of life. As such, they represent another therapeutic venue for circadian-based intervention in PD.

Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disease characterized by movement deficits, cognitive deterioration, and psychiatric symptoms. Sleep disturbances are common in HD, although not so thoroughly investigated as in other neurodegenerative disorders [167]. Emerging evidence points to circadian dysregulation in HD. Flattening of the circadian rhythm of melatonin secretion and circadian phase delay have been reported in patients with HD [168]. Circadian disruption has been observed in animal models of HD, such as transgenic R6/2 mice, specifically with their increased daytime activity and reduced nighttime activity [169]. Large animal models of HD including the transgenic sheep expressing a knock-in Huntingtin protein have also shown progressive circadian abnormalities during development, with some abnormal nocturnal behaviors analogous to human sundowning, especially seen in animals kept in an "HD-only" social flock grouping with similar animals, in contrast to animals kept with normal flocks who showed only minimal nocturnal behavioral changes [170]. These behavioral changes occurred on the background of abnormal expression of BMAL1 and Per2 clock genes in SCN, striatum, and motor cortex [169]. Although these reported abnormalities in circadian function provide the rationale for employing circadian-based interventions in the HD population, such interventions have not been systematically investigated among patients with HD. A few rather small studies examined the effects of exercise on sleep in HD and did not demonstrate robust favorable effects of the sleep metrics [171]. Pharmacological manipulations are effective in restoration of circadian oscillations in R6/2 mice [172]. Other non-photic zeitgebers, such as feeding schedules, positively impact rest-activity cycles in R2/6 mice model of HD, likely through the activation of the SCN-independent food-entrainable oscillator [173]. There is hope that further study of sleep disturbances in HD could inform future therapeutic approaches that could slow disease progression [174]; a very recent study has shown promise in rescuing locomotor function and disturbed circadian gene expression in a Drosophila model of HD, using melatonin and curcumin, a polyphenol contained in turmeric that activates BMAL1 and may have modulatory capabilities for circadian clock processes [175, 176], as well as other intracellular signaling pathways potentially mediating anti-inflammatory and antineoplastic effects.

Alzheimer's Disease

Alzheimer's disease (AD), the most common neurodegenerative disorder, has long been associated with sleep and circadian disturbances. Recent evidence strongly suggests a bi-directional relationship between AD and sleep/circadian disruption [177]. Sleep changes that accompany aging are accentuated among individuals affected by AD. Sleep becomes fragmented, leading to shorter TST; excessive sleepiness may develop with frequent napping, and sundowning often leads to behavioral changes and agitation. Alterations in sleep architecture in AD encompass less frequent and poorly formed sleep spindles and K complexes, reduced slow-wave sleep, and changes in the spectral properties of REM sleep [178, 179]. Burgeoning evidence demonstrates an increased risk of developing AD in individuals with a long-standing history of disturbed sleep [180, 181]. Circadian rhythms of sleep–wake cycles have reduced amplitude and delayed phase in individuals with AD [182]. Other biological rhythms, such as motor activity and CBT, also exhibit changes in circadian oscillations, likely reflecting degenerative changes of the SCN and the loss of ipRGCs [147, 183].

Patients with AD have reduced exposure to light and reduced levels of physical activity. Therefore, circadian-based interventions targeting light exposure and physical activity are important nonpharmacological treatment approaches in AD. Light therapy is the main circadian-based intervention for disturbances of sleep–wake cycles in patients with AD. Results of clinical investigations of light therapy in AD revealed conflicting results, which is likely due to the heterogeneity of the study cohorts and differences in study protocols. These investigations employed light therapy at 1000 to 10,000 lx over variable time periods (1–10 weeks) and time of day [184]. A majority of the studies documented improvements in the consolidation of

overnight sleep. Further studies employing larger cohorts and longer treatment exposure are needed to determine the optimal metrics of light therapy "dose," such as frequency, intensity, timing, and spectral properties of light. While melatonin may also have favorable effects on sleep in AD[185], the combined use of light therapy and melatonin may be an optimal approach in addressing circadian dysregulation in the AD population through their synergistic effects on the circadian system [186].

In summary, circadian dysregulation is common in neurodegenerative disorders, contributes to disturbances of sleep alertness in these populations, and may be influencing the biology of the neurodegenerative process itself. As such, the circadian system becomes an appealing therapeutic target for these disorders.

Conclusion

Many CRSWDs are still not widely recognized, and specific treatment regimens remain more as an art-of-medicine approach based on known aspects of circadian sleep–wake physiology rather than rigorous evidence for efficacy and tolerability from systematic controlled trials. Many of the treatment strategies discussed in this paper were performed in closely monitored laboratory-based studies with healthy individuals. Since controlled trial evidence is lacking for many CSWRDs, sleep medicine clinicians have been informed by theoretically based principles of circadian rhythm manipulation, along with clinical experience. The conceptual basis for treatment of CRSWDs is reasonably well-established, but the practical implementation of light, melatonin, and behavioral-based therapies require further study to optimize tailored individual and combination therapy regimens for the various disorders, including details of the duration of treatment, luminosity, dosage, and other administration details that can impact efficacy, tolerability, and adherence.

As clinical studies progress, further understanding of the genetic underpinnings of CRSWDs will be helpful to inform more rational biologically based therapeutic approaches. Just as the therapeutics of CRSWDs remain in their infancy, the promise of chronotherapeutic approaches to other diseases and disorders is also sure to progress as we continue to learn more about circadian rhythms and their system-wide synchronization between the brain and periphery. Temporal calibration for administration of therapeutics may become a standard throughout clinical medicine but will require substantial further research.

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Declarations

Disclaimer The contents of this review are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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