Chapter 10
Irregular Sleep-Wake Rhythm Disorder

Danielle Goldfarb and Katherine M. Sharkey

Introduction

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by persistent, erratic sleep-wake patterns. In patients with ISWRD, the typical circadian pattern is severely disrupted, and instead there is sleep fragmentation and a striking lack of sleep consolidation. In the most severe cases, it can be difficult to discern a single "main" sleep period on any given day. ISWRD occurs most commonly in individuals with neurodegenerative and neurodevelopmental disorders, patients with schizophrenia, and among those with traumatic brain injury. Internal and external factors implicated in the development of ISWRD include dysfunction of the suprachiasmatic nucleus (SCN) and its networks, abnormal SCN input, and disrupted environmental time cues (zeitgebers). Often a vicious cycle develops where one factor perpetuates another. For example, individuals with advanced dementia are often institutionalized in settings where they are exposed to less robust environmental cues compared to healthy, age-matched individuals, thereby magnifying the pathology.

Pathophysiology

The pathologic mechanisms of ISWRD have not been fully elucidated. It is hypothesized that disruption of any of the internal drivers (SCN and related networks) and/or external drivers (environmental and behavioral time cues) of circadian rhythms

D. Goldfarb
University of Arizona College of Medicine, Phoenix, AZ, USA

K. M. Sharkey (✉)
Department of Medicine and Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA
e-mail: katherine_sharkey@brown.edu

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can lead to its development. The integrity of the SCN and the monosynaptic pathway from the retina to the SCN, known as the retinohypothalamic tract, are crucial for proper circadian function. Abnormal SCN development or degeneration leads to the inability to produce circadian rhythmicity resulting in an inability to consolidate sleep and wakefulness. Much of what we know about the pathophysiology of circadian dysrhythmia derives from studies of neuroanatomy and neurophysiology in patients with dementia. For example, brain autopsies of patients with severe Alzheimer's disease (AD) reveal SCN degeneration, namely, neuronal loss and neurofibrillary tangle formation [1], likely contributing to circadian desynchrony.

Abnormal input to the SCN can be a result of impaired light input pathways and/or abnormal melatonin secretion. Within the retina, a small subset of specialized cells, called intrinsically photosensitive retinal ganglion cells (ipRGCs) [2, 3], which comprise only about 1–2% of the total retinal ganglion cells, play a crucial role. The ipRGCs relay information about ambient light to the SCN via the retinohypothalamic tract and contribute to many functions of the eye including sleep regulation, melatonin secretion and suppression, and the pupillary reflex [4]. Loss and pathology of ipRGCs have been shown in postmortem retinas of patients with AD [5] and in glaucoma [6].

Melatonin secretion by the pineal gland follows a circadian rhythm generated by the SCN and occurs only in dark environmental conditions during the biological night. The melatonin secretion pathway begins with retinal photoreceptors that transduce photic information (i.e., absence of light) via the retinohypothalamic tract to the SCN. In turn, ventral SCN neurons enervate neurons in the paraventricular hypothalamic nucleus (PVH) that traverse through the spinal cord to the superior cervical ganglion (SCG). Finally, noradrenergic SCG projections to the pineal gland act on beta-1-adrenergic receptors on pinealocytes to increase the activity of the rate-limiting enzyme required for melatonin synthesis—arylalkylamine-N-acetyltransferase—thus stimulating melatonin secretion. Melatonin binds to SCN receptors and decreases the circadian alerting signal during darkness, thereby promoting sleep. Conversely, when light is present, melatonin secretion is inhibited by decreasing the activating influences of neurons in the PVH nucleus [7]. Even relatively low ambient light levels can acutely suppress nighttime melatonin production. Suppression of melatonin secretion and phase shifting of the dim light melatonin onset (DLMO) are most sensitive to blue spectrum light ~460 nm [8]. Age-related anatomic and physiologic changes lead to decreased nighttime melatonin production, reduced rhythm amplitude, and changes in the timing of the melatonin rhythm [9]. The postulated causes for melatonin changes with aging are similar to those in ISWRD, including disruption of the SCN and its inputs, along with reduced environmental time cues [10]. Melatonin content in postmortem human pineal glands has been shown to be reduced with age [9].

Characteristic age-related changes in rest-activity circadian rhythms include lower amplitude [11], fragmentation and loss of rhythms [12], and decreased sensitivity to zeitgebers such as light exposure [13]. Aging is also associated with reductions in slow wave sleep and sleep efficiency and increases in nighttime awakenings [14]. Sleep disruption may contribute to behavioral disruption of circadian entrainment by increasing light exposure during typical sleep periods.

The eye is gaining increasing attention as a potential biomarker for neurodegenerative disease, specifically via retinal imaging. Besides loss of ipRGCs in AD, reduced retinal nerve fiber thickness has been identified through optical coherence tomography [15], providing additional support for disrupted light pathways. Furthermore, in their 2011 study, Koronyo-Hamaoui and colleagues demonstrated retinal amyloid beta (Aβ)—the peptide that comprises amyloid plaques found in the brains of AD patients—in postmortem eyes of eight AD patients and five suspected early-stage cases using specialized retinal imaging [16].

Genetic and epigenetic mechanisms that regulate the circadian clock and potentially contribute to dysrhythmias like ISWRD are a topic of active investigation. Generating circadian signals at the cellular level, several clock genes have been identified in mammals, including the positive regulators brain and muscle ARNT-like 1 (BMAL1), *Circadian Locomotor Output Cycles Kaput* (CLOCK), and neuronal PAS domain protein 2 (NPAS2) and the negative regulators cryptochromes 1 and 2 (CRY1/2) and period 1, 2, and 3 (PER1/2/3), all of which are expressed in SCN neurons [17]. Individual mutations in any of these genes cause aberrant circadian rhythmicity. For example, a study of BMAL1 knockout mice demonstrated immediate loss of rhythmicity in the absence of a light-dark cycle [18]. BMAL1 may play a particularly significant role in circadian dysrhythmia related to AD: in mouse models, Aβ induces BMAL1 degradation in neuronal cells [19] and hence may contribute to circadian disruption. Furthermore, Cermakian and colleagues [20] showed asynchronous clock gene expression in other (non-SCN) brain regions in AD patients compared to controls.

Disrupted environmental and behavioral inputs to the clock, i.e., zeitgebers such as light exposure, social cues, activity, and mealtimes, influence the period, phase, and amplitude of circadian rhythms [21]. Without sufficient exposure to timed light, the biological clock becomes desynchronized with the solar day, resulting in deleterious effects on various physiological functions, neurobehavioral performance, and sleep [8]. Older adults and, to an even greater extent, institutionalized elderly, are less likely to be exposed to robust daytime light [22]. Ancoli-Israel and colleagues demonstrated that lower daytime light levels contribute to increasingly abnormal circadian rhythms as measured by actigraphy and are associated with an increase in nighttime awakenings, even after controlling for the level of dementia [23].

Gehrman and colleagues [24] demonstrated that rest-activity patterns decline initially in earlier stages of dementia, with a resurgence of rhythmicity in moderate dementia, followed by subsequent decline in severe dementia. The authors posit that the two sources of synchronization of rhythms, the endogenous output by the SCN and entrainment by the environment, give rise to a three-stage model of rest-activity rhythm changes in dementia. In the early stages, SCN damage results in a decline in rhythmicity. Eventually, environmental cues take on a larger role contributing to a resynchronization of circadian rhythms. When dementia becomes severe, environmental cues lose their potency.

Over the last decade, there has been greater recognition that sleep and circadian rhythm abnormalities may be early manifestations of AD, even preceding cognitive decline. In a large actigraphy study of over 1200 healthy women, Tranah and colleagues [25] demonstrated that decreased amplitude and weaker circadian

rest-activity rhythms were associated with an increased risk of mild cognitive impairment or dementia within the subsequent 5 years. In a recent actigraphy study of over 2700 community-dwelling older males, rest-activity rhythm changes, including lower amplitude and rhythm robustness, along with phase-advanced acrophase, were associated with clinically significant cognitive decline [26].

Finally, though still a novel area of investigation, there is increasing interest in the link between circadian system malfunction, early-life insults (i.e., severe gestational stress, maternal immune activation, and fetal hormonal milieu alterations), and the development of neuropsychiatric diseases in adulthood. For an excellent discussion on this topic, see the review by Marco and colleagues [27]. Further understanding of the fetal-maternal environment, brain development, and circadian rhythms may ultimately support the discovery of innovative therapeutic pathways.

Clinical Features, Epidemiology, and Diagnosis

Individuals with ISWRD present with either nighttime insomnia, daytime sleepiness, or both. Sleep patterns are unpredictable, and some patients rarely spend a full hour awake during the day or sleep continuously for more than an hour during the night [28]. Initial caregiver reports may describe frequent brief naps, dozing, or nodding off throughout the daytime, along with difficulty with sleep initiation at a conventional time and increased nighttime wakefulness. Though sleep patterns are erratic, overall total hours of sleep may be normal for age in patients with ISWRD. Nevertheless, the irregular sleep patterns can lead to negative repercussions, including nocturnal wandering and falls [29]. Furthermore, because ISWRD patients' irregular sleep patterns cause significant disruption to caregivers' sleep, the disorder is a common cause of institutionalization [29].

Populations affected by ISWRD are diverse and, in addition to what is described above, include those with neurodevelopmental disorders of childhood and schizophrenia. As well, ISWRD has been identified in individuals with traumatic brain injury. Among caregivers, irregular sleep-wake patterns may not be perceived as a separate issue from the underlying disorder or may simply be described as insomnia. Thus, ISWRD is likely to be underdiagnosed unless clinicians make specific inquiries about it [29].

Making the diagnosis of ISWRD requires sleep-activity monitoring for 7–14 days with logs, typically completed by a caregiver and, if possible, actigraphic monitoring. Findings include significant fragmentation without identification of a major sleep period (see Fig. 10.1). According to the International Classification of Sleep Disorders [29], there must be at least three brief sleep periods during a 24-hour period, and symptoms must be present for at least 3 months to make the diagnosis.

Abnormal rest-activity patterns are a common and progressive feature in neurodegenerative diseases such as AD, and actigraphic findings show that increased fragmentation and decreased amplitude of activity correlate with dementia severity [30]. Nurses caring for hospitalized patients in a geriatrics ward observed a blunted

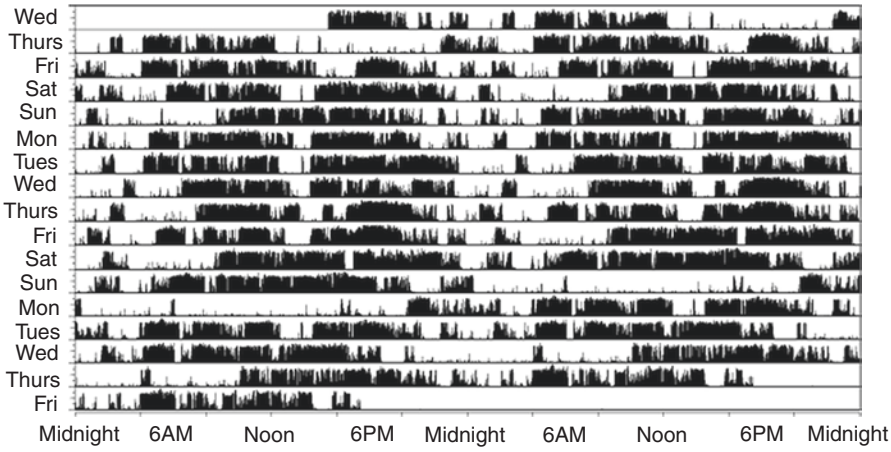

Fig. 10.1 Actigraphy in a patient with ISWRD: Features of irregular sleep-wake rhythm disorder (ISWRD) are illustrated in this double plot of 17 days of wrist actigraphy in a patient with ISWRD associated with neurologic disease. The patient had multiple sleep-wake episodes across 24 hours with multiple wake episodes at night and irregular sleep periods during the day. In this patient, sleep mostly occurred at night, consistent with his efforts to adhere to a conventional sleep-wake schedule

amplitude of rest-activity rhythms that corresponded with abnormal patterns of core body temperature rhythm in patients with vascular dementia or AD compared to age-matched controls [31]. Decreased rest-activity amplitude is also correlated with a higher degree of cognitive impairment in community-dwelling older adults [32].

Sleep difficulties are common in neurodevelopmental disorders of childhood [33], often with co-occurring circadian rhythm disorders. Comorbid ISWRD in youngsters with developmental disorders can be associated with reports from parents and/or caregivers that their child sleeps or naps inappropriately, falls asleep too early at night, awakens too early in the morning, and/or cannot stay awake during the day for activities [29]. Despite the profound impact of irregular sleep-wake patterns on families caring for children with developmental disorders, there is a paucity of research on ISWRD in children and adolescents. Nevertheless, ISWRD has been described in Angelman syndrome [34], Smith-Magenis syndrome [35], neuronal ceroid lipofuscinosis [36], and Williams-Beuren syndrome [37]. A case of ISWRD has also been reported in a congenitally blind, neurodevelopmentally delayed child [38]. Furthermore, abnormalities in melatonin rhythms associated with irregular sleep-wake behavior have been shown in Smith-Magenis syndrome [35] and Williams-Beuren syndrome [37]. Little is known about the clinical course of childhood ISWRD or the consequences of irregular sleep-wake patterns during critical developmental periods. One study of older adults with intellectual disabilities found that, compared to older adults with normal cognitive function, the sleep-wake rhythm in the former group was less stable and more fragmented [39].

ISWRD has been described in schizophrenia, particularly in individuals with "positive" symptoms [40]. Bromundt and colleagues [41] studied 14 middle-aged individuals with schizophrenia treated with antipsychotics using actigraphy and salivary melatonin in addition to neurocognitive testing. Participants with lower circadian amplitude had more fragmented sleep, atypical melatonin secretion patterns, and worse cognitive performance. Vigano and colleagues also observed lower nighttime melatonin levels and blunted melatonin rhythm amplitudes in patients with schizophrenia [42]. It is noted that melatonin levels and rhythmicity in this population are difficult to interpret as the effects of antipsychotic medications on melatonin are poorly understood.

Circadian rhythm disorders also occur after traumatic brain injury (TBI). Ayalon and colleagues [43] studied 42 patients with mild TBI who had complaints of insomnia (34 with difficulties falling asleep or waking up and 8 with sleep maintenance insomnia) and found that 7 had ISWRD and 8 had delayed sleep-wake phase disorder (DSWPD). Compared to DSWPD individuals, those with ISWRD demonstrated a lower amplitude in oral temperature rhythm and 3 of 7 lacked a daily temperature rhythm entirely. The mechanisms of circadian rhythm disturbance in TBI are not well understood; however, there are likely multiple factors at play. Duclos et al. [44] provide a review of possible pathophysiologic mechanisms including a maladaptive immune response, dysregulated clock genes, and confounding effects of acute hospitalization, pain, and anxiety.

Other causes of acquired damage to the SCN contributing to the development of ISWRD have been described. One report detailed posttraumatic irregular sleep-wake rhythm in a 38-year-old woman after she sustained a gunshot wound that damaged her SCN and bilateral optic nerves [45]. Another case report describes an individual who developed ISWRD in association with a prolactin-secreting pituitary microadenoma that impinged upon the SCN [46].

Management

ISWRD treatment aims to restore SCN time cues to decrease sleep fragmentation, consolidate the sleep-wake pattern, and improve circadian rhythm amplitude. Strengthening external circadian signals helps resynchronize the pacemaker, allowing the body to anticipate predictable physiologic and behavioral needs intrinsically tied to day and night. Interventions include light therapy and timed exogenous melatonin administration, as well as directed physical and social activity.

Bright light exposure has been studied to treat irregular sleep-wake patterns in institutionalized older adults, though in most investigations the patient sample was heterogeneous and the participants rarely had formal ISWRD diagnoses. For example, Mishima and colleagues [47] compared bright light (between 3000 and 5000 lux) administered for 2 hours between 9:00 and 11:00 AM in 14 hospitalized patients with dementia and sleep disturbance. After 4 weeks of daily treatment, patients in the bright light group slept less during the day and more at night. Another

trial of bright light in 10 elderly patients with severe dementia treated with 5000–8000 lux for 45 minutes daily for 4 weeks between the hours of 8:00–10:00 AM showed behavioral improvements as measured with the Cohen-Mansfield Agitation Inventory (CMAI) and Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [48].

Augmented light exposure for 45 minutes to 2 hours at levels ranging from 1000 to 8000 lux has been tested in several other studies of elderly nursing home residents with dementia with irregular sleep-wake patterns suggestive of ISWRD, with most studies demonstrating positive effects of bright light, specifically more consolidated sleep at night and less sleep during the day [49–55]. In the 2015 American Academy of Sleep Medicine clinical practice guidelines for the treatment of circadian rhythm sleep wake disorders [56], bright light therapy for ISWRD is recommended among elderly patients with dementia. Side effects from light therapy are generally mild [57] and if it can be provided with relatively low cost and labor for caregivers, the behavioral benefits likely outweigh any associated symptoms.

The AASM clinical practice guidelines specifically recommend against using hypnotics or melatonin to treat ISWRD in elderly patients with dementia [56]. Hypnotic medications increase risk of falls and daytime sleepiness in older adults and there is no data supporting their use in ISWRD; hence, they should generally be avoided. Exogenous melatonin has been tested for ISWRD in older patients with dementia, but has not been shown to regulate sleep-wake patterns better than placebo, and is associated with untoward mood and behavioral outcomes. For example, in a study of 157 AD patients treated with 2.5 mg slow-release melatonin, 10 mg melatonin, or placebo, melatonin failed to improve actigraphically estimated total sleep time (TST) after a 2-month treatment period [57]. This lack of efficacy, combined with another study showing that elders with dementia in an assisted living facility who were treated with 2.5 mg of melatonin in the evening had an increased incidence of negative affect and withdrawal [58], resulted in the recommendation against routine use of melatonin for ISWRD in elderly patients with dementia.

In contrast, data support the use of appropriately timed exogenous melatonin to treat children and adolescents with neurodevelopmental disorders and ISWRD [56]. A double-blind, randomized controlled trial of 16 youngsters ages 3–16 years old with autism spectrum disorder compared 3 months of evening melatonin administration versus placebo in a crossover design [59]. Parents reported shortened sleep onset latency and increased TST with melatonin (dose range 2–10 mg) compared to placebo. Improvement in sleep duration was also observed in a small open trial testing 3 mg of melatonin administered each evening at 6:30 pm to children with severe developmental disabilities and disrupted sleep wake patterns [60]. Finally, in the largest study to date of 125 youngsters with autism spectrum disorder, extended release melatonin, starting at 2 mg and increased to 5 mg, increased parent/caregiver reported sleep duration by nearly 1 hour (compared to 9 minutes with placebo) and shortened latency to sleep onset by 39 minutes, compared to 12.5 minutes with placebo [61]. Most studies using melatonin in youths with ISWRD reported minimal, mild side effects, such as increased daytime sleepiness, with high patient and caregiver treatment acceptability. Nevertheless, clinicians considering melatonin

administration to treat ISWRD in children with neurodevelopmental disabilities should be aware of a single nucleotide polymorphism (SNP) of CYP1A2 (Cytochrome P450 Family 1 Subfamily A Member 2) that has been associated with slow melatonin metabolism yielding extremely high daytime levels in youngsters with autism spectrum disorder [62, 63]. Moreover, experts contend that because no long-term safety studies of exogenous melatonin administration in adolescents are available, its use should be reserved for situations with significantly disturbed sleep-wake patterns where the benefits clearly outweigh possible risks [64].

Another strategy for treating irregular sleep-wake patterns associated with severe circadian dysregulation is to halt pineal melatonin secretion by administering a β1-antagonist in the morning and supplementing with exogenous melatonin in the evening. This treatment was tested in 10 children with Smith-Magenis syndrome who displayed a near inversion of typical circadian entrainment at baseline. Use of this regimen increased sleep time at night, improved sleep quality, and reduced problematic behaviors during the day [65].

There are no well-established, evidence-based treatments specifically for ISWRD in patients with schizophrenia, in part because ISWRD is rarely diagnosed formally in patients with psychiatric illness. Circadian-based treatments for irregular sleep-wake patterns have been studied most often in patients with bipolar disorder, and strategies such as bright light therapy and stabilizing sleep patterns are effective both for improving sleep and stabilizing mood [66, 67]. Treatment studies for circadian dysregulation—including ISWRD—in psychiatric illness are needed urgently. Promising therapeutic pathways include bright light therapy, sleep deprivation or restriction, use of the melatonin agonist and serotonin-2C antagonist agomelatine, and further study of the circadian stabilizing properties of established medications, e.g., selective serotonin reuptake inhibitors, lithium, valproic acid, and more novel pharmacologic agents, e.g., ketamine and brexanolone.

Conclusion

ISWRD is a debilitating syndrome in which patients have multiple, irregular sleep-wake episodes across the day. It is observed most commonly in patients with neurodevelopmental and neurodegenerative disorders as well as those with neurologic trauma or schizophrenia. ISWRD is disruptive to successful treatment of comorbid conditions and poses significant challenges to the caregivers of patients with this CRSWD. Disruption of input to and output from the SCN is believed to underlie the circadian desynchrony in ISWRD. Thus, treatment strategies like bright light therapy and exogenous melatonin administration focus on strengthening signaling to and from the internal clock. In addition to better syndrome-specific therapies for ISWRD and for CRSWDs in general, more clinical research is needed to establish optimal “doses” of behavioral and pharmacologic treatments. Best practices and treatment guidelines are needed to guide duration of treatment and the use of

combination therapies. Future research should also determine whether prevention and treatment can lead to better outcomes of the comorbid neurologic disorders that often accompany ISWRD.

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