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Irregular Sleep-Wake Rhythm Disorder



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KEYWORDS

• Sleep • Circadian • Irregular sleep-wake • Melatonin • Light therapy

KEY POINTS

- Irregular sleep-wake rhythm disorder is characterized by lack of clear major sleep-wake pattern.
- The disorder affects children and adults and is common in individuals with neurodevelopmental delay and neurodegenerative and psychiatric disorders.
- Actigraphy and sleep diaries are used in establishing a diagnosis.
- Treatment modalities encompass use of melatonin, supplemental light exposure, and behavioral modifications aimed at consolidation of sleep-wake rhythm.

IRREGULAR SLEEP-WAKE RHYTHM DISORDER

Patients with irregular sleep-wake rhythm disorder (ISWRD) report difficulties synchronizing their sleep time with that of societal norms.¹ The absence of clear circadian rhythm of sleep-wake leads to irregular periods of sleep during both day and night.¹ As such, patients with this disorder experience notable daytime sleepiness at random times of the day, not associated with a physiologic homeostatic or circadian rhythm pattern. A patient has irregular fragmented sleep over the 24-hour cycle, with the longest sleep periods less than 4 hours each.² The longest sleep times usually are from 2:00 AM to 6:00 AM. Total sleep time usually is within the normal range for age within a 24-hour period; however, these patients are unable to consolidate their daily sleep into a single 6-hour to 8-hour period.¹ As a result, this disorder is characterized by a lack of a clearly defined circadian sleep and wake cycle. These patients frequently are in conflict with societal norms and daytime activities. This frequently results in overall sleep restriction because there is an inability to attain adequate sleep of 6 hours to 8 hours during usual nighttime/sleep hours.³

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PREVALENCE

The prevalence of this disorder is unknown but it is estimated to be rare.¹ There are no known gender differences; however, the disorder is prevalent in the elderly, especially among those affected by neurodegenerative disorders. It also commonly found in children with developmental delay.

PATHOGENESIS

The exact pathogenesis of ISWRD is not fully understood; however, it is believed that a dysfunction within the central processes involved in generation and maintenance of circadian rhythms is responsible.³ Depending on the disorder type, the development of irregular sleep-wake patterns may be due to changes within the suprachiasmatic nucleus (SCN) or changes to the input that is received by the SCN. A reduction in exposure to zeitgebers, such as light and/or impaired transmission of light signaling to the SCN, as well as changes in melatonin secretion may be culprits of ISWRD. Low daytime light exposure has been associated with increased wake times at night.^{4,5} Alterations in social environment also may be responsible for ISWRD. Irregular social schedules, decreased mobility, and adverse effects of medications on sleep as well as increased daytime napping all may play a role. Genetic factors have been implicated in disorders associated with ISWRD, including neurodegenerative disorders, such as Alzheimer disease (AD).²

SYMPTOMS

Individuals with ISWRD complain of insomnia or excessive sleepiness associated with multiple (3 or more) irregularly scheduled naps throughout the day, each of varying duration. The insomnia frequently is a sleep maintenance-type insomnia.³ This can be one of the more onerous disorders for caregivers to deal with. In addition, individuals with this disorder complain of inability to participate in usual daytime activities for prolonged periods of time due to their excessive daytime sleepiness.²

DIAGNOSIS

Actigraphy along with a sleep diary over a 7-day to 14-day period is the most useful diagnostic option currently.¹ An actigraph shows a disturbed low-amplitude circadian rhythm with a loss of a normal diurnal sleep-wake patterns (**Fig. 1**). The actigraph also shows at least 3 distinct sleep periods over a 24-hour period. It is imperative that this disorder be distinguished from other sleep disorders associated with poor sleep hygiene and voluntary maintenance of an irregular sleep schedule, such as shift work or jet lag.¹

TREATMENT

Measures aimed at consolidation of the sleep-cycle are at the core of interventions for ISWRD. The goal is to enhance the amplitude of circadian rhythms and align them to the external physical environment.¹ Treatment involves timed supplemental light exposure, melatonin, and behavioral interventions (**Table 1**). Mixed modality approaches can be used and emphasize use of simultaneous interventions that may produce more robust circadian amplitude and consolidation of sleep-wake cycles. Strategies may include increasing exposure to bright light and staying

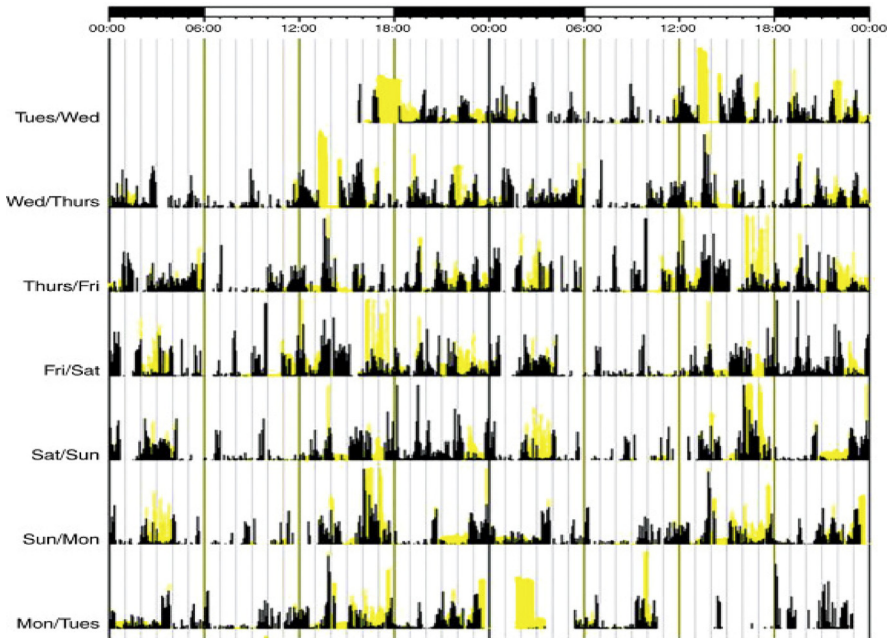


Fig. 1. Typical actigraph seen in patients with ISWRD. (From Malkani R, Zee PC. Basic circadian rhythms and circadian sleep disorders. In: Atlas of Sleep Medicine, 2014, 2nd edition; with permission.)

out of the bed during the day, enforcing strict bedtime routines, eliminating noise, and reducing lighting in the bedroom overnight. In children and adults with psychomotor developmental delay, melatonin in doses of 2-mg to 20-mg may improve and consolidate sleep patterns as well as reduce sleep during daytime. Similarly, melatonin, 2 mg, administered at bedtime resulted in improved sleep in individuals with schizophrenia. Melatonin should be avoided in elderly patients with dementia.² These individuals may benefit from structured daily activities, bright light exposure, and increased daytime social interactions to improve alertness during the day. Overall, sedatives are not recommended for the treatment of ISWRD. Exercise may be helpful during the daytime; however, exercise alone may not sufficiently treat the disorder. Recent evidence suggests that increasing exposure to a cognitively enriched environment during the daytime may improve symptoms significantly.³ Studies also suggest that a combination of bright light therapy, chronotherapy, and vitamin B₁₂ may be beneficial.¹ Light exposure of 3000 lux to 5000 lux for 2 hours every morning over 4 weeks can improve daytime alertness but may not be as effective in consolidating nighttime sleep. This light exposure may also reduce sundowning behavior in AD patients.³

PRACTICE GUIDELINES FROM THE AMERICAN ACADEMY OF SLEEP MEDICINE

There is a clear need for the development of novel treatment modalities, and there is ongoing research to address these concerns.³ Based on the current limited evidence

Table 1 Current treatment recommendations for irregular sleep-wake rhythm disorder		
Population	Treatment	Results/Outcomes
Elderly with and without dementia	Light	Daytime light exposure (2500 lux) may increase total sleep time at night. ⁶
	Melatonin	Randomized controlled trials have shown no improvement in sleep and may worsen mood. ^{7,8}
	Mixed-modality treatment	Morning bright light (>10,000 lux), low-level physical activity, structured bedtime routine, and reduction of light and noise at night can improve sleep. ^{5,9}
Children	Light	Morning bright light (4500 lux) normalized the sleep-wake cycle. ¹⁰
	Melatonin	Doses ranging from 1 mg to 5 mg have improved sleep-wake patterns. ¹¹
	Mixed-modality treatment	Environmental modification, positive bedtime routines, calming activities, and stimulus control are recommended. ^{12,13}
Psychiatric Disorders	Light	Daytime bright light exposure (up to 10,000 lux) improved sleep-wake cycle. ¹⁴
	Melatonin	Melatonin, 2 mg, at bedtime improved sleep. ¹⁵

available in the literature, however, the American Academy of Sleep Medicine (AASM) has recommended the following practice guidelines:

1. Clinicians should treat ISWRD in elderly patients with dementia with light therapy. (WEAK EVIDENCE)
2. Clinicians should avoid the use of sedating or sleep-promoting medications to treat elderly patients with dementia and ISWRD. (STRONG EVIDENCE)
3. Clinicians should avoid the use of melatonin as a treatment of ISWRD in elderly patients with dementia. (WEAK EVIDENCE)
4. Clinicians should use strategically timed orally administered melatonin as a treatment of ISWRD in children and adolescents with neurologic disorders. (WEAK EVIDENCE)
5. Clinicians should avoid the use of combined treatments consisting of light therapy in combination with melatonin in elderly ISWRD patients with dementia. (WEAK EVIDENCE)
6. There are no specific recommendations from AASM for the use of the following treatment options to manage ISWRD:
 - a. Prescribed sleep-wake scheduling
 - b. Timed physical activity/exercise
 - c. Strategic avoidance of light
 - d. Wakefulness-promoting medications
 - e. Other somatic interventions

IRREGULAR SLEEP-WAKE DISORDER IN SPECIAL POPULATIONS

ISWRD frequently is observed in neurodegenerative disorders and brain injury.² It also is associated with children with psychomotor developmental delay and autistic spectrum disorders. In these disorders, irregular sleep and wake patterns are believed associated with dysfunction in the central processes associated with the maintenance of circadian rhythms.³ Angelman syndrome and Smith-Magenis syndrome are examples of child neurodevelopmental disorders characterized by irregular sleep pattern

and inversion of the sleep-wake cycles that may go along with decreased amplitude of melatonin rhythm. Neurodegenerative disorders, such as dementias, are associated with ISWRD. Elderly individuals with AD may experience severe sleep fragmentation with low circadian rhythm amplitude, especially if they have symptoms of sundowning. Elderly individuals in nursing homes also may experience similar disorders, which may be due to a lack of regular exposure to bright light and social schedules.²

Older Adults With and Without Dementia

Up to 70% of older adults complain of sleep disturbances from irregular sleep-wake cycles.¹⁶ The prevalence of irregular sleep-wake cycle is even higher in a population of AD and related dementias. These individuals have diminished amplitude of the rest-activity rhythm, with poorly consolidated sleep and frequently inverted sleep-wake cycles. Evidence suggests a reduction in neuronal activation of the SCN in older adults. Melatonin rhythm becomes less robust in AD. These changes lead to an alteration of circadian rhythm patterns and regularity. Ultimately, the SCN becomes less responsive to light leading to less entrainment of the sleep-wake cycle.¹⁷ This circadian misalignment can have significant consequences on sleep.

Assisted living facilities tend to provide limited bright light exposure to their residents; middle-aged adults experience approximately 60 minutes of bright light exposure during the day whereas older adults especially with dementia and/or in nursing homes can be exposed to less than 2 minutes of bright light daily.¹⁸ Even among older adults who deny suffering any sleep disturbance, it is clear that irregular disrupted sleep-wake cycles can significantly impair cognitive function.¹⁹ Assisted living facilities would benefit from bright lighting to improve irregular sleep-wake rhythms in the elderly. Riemersma-van der Lek and colleagues⁷ evaluated assisted living facilities that were randomly assigned to emit bright white light (1000 lux) or dim light (300 lux) in their ceiling fixtures within the common areas during the daytime. Individuals in brightly lit facilities had lower total sleep time, reduced cognitive deficits, and improved depression symptoms at 6 weeks and 6 months. In this population, non-pharmacologic interventions to improve the sleep-wake cycle was key to improving quality of life.⁵ Specifically, bright light exposure (especially sunlight) increased physical activity and structured bedtime routines, and elimination of nighttime noise and light played crucial roles in improving irregular sleep-wake cycles. Bright light exposure to treat ISWRD is most effective in individuals with relatively good vision.²⁰ There seems to be little role for pharmacologic interventions in this population. A meta-analysis assessing the benefits and risks of sedative/hypnotic interventions in this population with irregular sleep-wake cycles showed that the benefits do not clearly outweigh the significantly increased risk associated with the constant use of these medications.²¹ There may be a role for melatonin, however, in treating the ISWRD. Riemersma-van der Lek and colleagues⁷ found that a combination of bright light exposure and melatonin treatment led to improved sleep efficiency, reduced nighttime activity, and improved cognitive and behavioral function.⁷ The AASM, however, currently does not recommend combination therapy.³

In addition to improving sleep, both cognition and behavior are improved when light exposure is optimized among older adults with dementia. Light exposure, especially in the evening, can decrease nighttime activity significantly, including eloping/walking. In addition, agitated behaviors and sundowning were significantly improved with 1 hour of bright light (10,000 lux) every morning for 2 weeks.^{22,23} These findings are not unique to AD. Studies looking at other dementia types, including vascular dementia, showed similar findings.²⁴ The time of day of light exposure seems to have a significant effect as well. Morning light leads to improved sleep better than evening light

exposure and all-day light exposure.²⁵ In general, there are minimal gender differences; however, evidence suggests that older women have a better improvement in depressive symptoms with morning light exposure compared with older men.²⁵

Overall, it is clear that supplemental light exposure as an intervention to treat ISWRD in the elderly with and without dementia can be beneficial. In addition, strategic light exposure in long-term care/assisted living facilities is important to improve sleep, depression, behavior, and cognition in older adults with dementias.²⁶

Parkinson Disease

Parkinson disease (PD) is a movement disorder characterized by tremors, slowness, and stiffness. In addition to these motor manifestations of the disease, several nonmotor manifestations of PD negatively affect quality of life and safety of PD patients. Among these nonmotor manifestations, impaired sleep and alertness are common. Excessive sleepiness affects up to 30% of patients with PD.²⁷ Sleep fragmentation is the most common sleep disturbance in PD. These impairments of alertness and sleep continuity are the bases for irregular sleep-wake rhythms in PD. The etiology of poor sleep and poor alertness in PD is multifactorial and encompasses overnight emergence of motor symptoms, effects of dopaminergic medications, coexistent primary sleep, and psychiatric disorders as well as effects of the primary neurodegenerative process underlying PD. Circadian dysfunction has emerged as a novel factor underlying irregular sleep-wake rhythms in individuals with PD. Circadian melatonin rhythm, which is an accepted marker of the endogenous circadian system, is dampened in individuals with PD.²⁸ This observation is suggestive of low circadian amplitude and has provided an opportunity for development of circadian-based interventions that target impaired sleep-wake cycles in PD. In this regard, several studies have documented beneficial effects of light therapy on sleep quality and sleepiness in PD.^{29–31}

Psychiatric Disorders

Individuals with psychiatric disorders, such as bipolar disorder and schizophrenia, frequently report sleep disturbances. Poor control of and more exacerbations of these disorders are associated with irregular sleep-wake rhythm. Irregular sleep is one of the most important signs of the emergence of a hypomanic/manic episode³² and schizophrenia exacerbations.^{33,34} A recent review showed that individuals that are high risk for bipolar disorder report persistent irregularity in their sleep-wake rhythms.³⁵ As a result, irregular sleep patterns could be used as a marker to identify changes in disease patterns, leading to exacerbations.³² Further research is necessary to fully characterize this relationship and to determine the best intervention options for this population.

Irregular Young Adult Sleepers

ISWRD also has the substantial consequences on the general population regardless of age or mental health disorders. Irregular sleep-wake patterns in a young relatively healthy undergraduate population can have significant effects on academic performance.³⁶ Young individuals with adequate sleep duration but irregular sleep patterns show poorer performance in real-world social and academic settings compared with regular sleepers. In addition, individuals with irregular sleep tend to have delayed sleep timing and more daytime naps, which can perpetuate the irregularity of sleep-wake patterns. The irregular sleep also can have effects on sleep physiology because there is evidence of delayed onset of melatonin secretion despite appropriate circadian and homeostatic cues.³⁶

Autism

Children with autism tend to have irregular sleep-wake patterns, including early awakening in the morning and later sleep times in the evening.³⁷ These children tend to have significant variability in total daily sleep time with large day-to-day variations. These sleep concerns tend to be worse in children younger than 4 years of age. Nighttime awakening with significant nighttime activity frequently is reported. Children with autism also frequently take daytime naps, regardless of age. This variability in sleep leads to irregular sleep-wake patterns and fragmented sleep duration.³⁷ These children are much less likely to show signs of delayed sleep-phase syndrome or advanced sleep-phase syndrome. As a result, a clear characterization of sleep patterns in children with autism has yet to be defined. Children with autism seem to have a bifurcation of the sleep-wake cycle with increased sensitivity to external noise and irregular sleep onset and offset.³⁷ This may be due to an altered balance of the circadian and homeostatic signals associated with sleep. Overall, children with autism tend to have shorter sleep periods over a 24-hour period compared with typically developing children.^{38,39}

Animal studies show that the disturbance in circadian rhythm in autism may be related to dysfunction in the serotonergic system in the brain.^{39,40} There is a reduced serotonin transporter binding capacity in children with autism; this may be the result of a primary deficit in melatonin synthesis, leading to accumulation of upstream serotonin. As a result, exogenous melatonin administration may be beneficial and therapeutic. With older age, the irregular sleep pattern begins to improve but tends to remain a significant trait of the disorder throughout the life span.

SUMMARY

In conclusion, ISWRD is considered a rare disorder, which is concentrated in specific populations with comorbid neurologic/psychiatric disorders. This disorder most commonly is noted in elderly patients with dementias but also is commonly observed in young children with notable neurologic disorders, such as autism spectrum disorder. Researchers have suggested that ISWRD likely is a manifestation of dysfunction of the sleep-wake-generating mechanisms within the brain. Because of the rarity of this disorder as well as the heterogeneity of comorbid neurologic conditions among individuals with ISWRD, a clear characterization and understanding of the underlying mechanisms have eluded researchers to this point. As a consequence, the treatments options available currently remain limited. Currently, the best options for treatment of this disorder are light therapy among the elderly and melatonin therapy in younger individuals with neurologic disorders. The focus of ISWRD research currently is to find novel treatment interventions that can improve daytime function and cognition in individuals with this disorder.

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