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Review

The Effect of Blindness on Biological Rhythms and the Consequences of Circadian Rhythm Disorder

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Abstract

Various physiological systems and behaviors such as the sleep-wake cycle, vigilance, body temperature, and the secretion of certain hormones are governed by a 24-hour cycle called the circadian system. While there are many external stimuli involved the regulation of circadian rhythm, the most powerful environmental stimulus is the daily light-dark cycle. Blind individuals with no light perception develop circadian desynchrony. This leads to non-24-hour sleep-wake rhythm disorder, which is associated with sleep-wake disorders, as well as mood disorders and loss of appetite and gastrointestinal disturbances due to disrupted circadian hormone regulation. As the diagnosis is often delayed because of under-recognition in clinical practice, patients must cope with varying degrees of social and academic dysfunction. Most blind individuals report that non-24-hour sleep-wake rhythm disorder affects them more than blindness. In the treatment of totally blind patients suffering from non-24-hour sleep-wake rhythm disorder, the first-line management is behavioral approaches. Drug therapy includes melatonin and the melatonin agonist tasimelteon. Diagnosing blind individuals' sleep disorders is also relevant to treatment because they can be improved with the use of melatonin and its analogues or by phototherapy if they have residual vision. Therefore, assessing sleep problems and planning treatment accordingly for individuals presenting with blindness is an important issue for ophthalmologists to keep in mind.

Keywords: Biological rhythms, circadian rhythm, blindness, light, melatonin

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Introduction

All living things have a multitude of biological rhythms occurring at different frequencies and periods, ranging from the cellular level to the physiological and social behavioral levels.[1] In humans, biological rhythm frequencies spanning nearly all segments of time have been described, such as electroencephalogram waves that oscillate by the second, 24-hour sleep-wake rhythms, the weekly pattern of urinary 17-ketosteroid excretion, and other rhythms that occur monthly, annually, or even every 10 years, like the appearance of some sunspots.[2] Among these biological rhythms, circadian rhythms (referring to a 24-hour period) are perhaps the most well studied. Human physiology and behavior are governed by a 24-hour circadian rhythm. The sleep-wake cycle, attention, behavior patterns, and hormone secretion are just a few examples of biological systems regulated by the circadian cycle. This rhythm is spontaneously adjusted by the suprachiasmatic nucleus in the anterior hypothalamus, which is an internal rhythm regulator.[3] In most people, this circadian rhythm is slightly longer than 24 hours and is adjusted daily to the solar rhythm of 24 hours according to environmental cues. The most important environmental cue for synchronization is light. Daily retinal exposure to light is needed to adjust the circadian rhythm to 24 hours.[4] Except for those with jetlag or shift work, this daily synchronization occurs with no problem in people with good eyesight. However, people with bilateral vision loss or blindness become desynchronized due to the lack of light input to the suprachiasmatic nucleus.[5]

In this review, we aimed to examine the changes in circadian rhythm associated with the lack of light input in blind individuals, as well as the physical and mental consequences of and treatment approaches to these changes, in light of the current literature. To better understand the physiopathology, we first examine the relationship between light, melatonin, and circadian rhythm.

Light, Melatonin, and Circadian Rhythm

Circadian rhythm refers to biological, physiological, and behavioral changes in an organism over a period of approximately one day. In this sense, the sleep-wake cycle is the most basic and definitive circadian rhythm in the human body.[6] The mammalian circadian system also includes the retina, the retinohypothalamic pathway, the pineal gland, and the suprachiasmatic nucleus. However, the structure responsible for regulating the circadian rhythm is the suprachiasmatic nucleus in the anterior hypothalamus.[3] The main purpose of this region is to ensure that the physiological functioning and internal equilibrium of the organism work in harmony with the external environment and that rhythmic functions are carried out regularly by maintaining that harmony in different conditions. The suprachiasmatic nucleus receives many external stimuli (zeitgeber) to adjust circadian rhythm and diurnal rhythm. Light is the most important rhythm regulator among these external stimuli.[7] The environmental light-dark cycle is a key factor in the regulation of circadian rhythm. Light is detected by melanopsin-containing photosensitive retinal ganglion cells, which project via the retinohypothalamic pathway to the suprachiasmatic nucleus. The light stimulus is transmitted through the superior cervical ganglion to the pineal gland via complex neural networks.[8] In this way, light suppresses the synthesis of melatonin, a pineal hormone. The synthesis and release of melatonin is stimulated at night in the dark and suppressed by light during the day.[9] Exposure to light at night causes a decrease in plasma melatonin levels through this mechanism. Melatonin suppresses neuronal firing in the suprachiasmatic nucleus, resulting in sleep induction and maintenance. Exogenous melatonin intake produces a hypnotic effect.[10] Depending on the timing of light exposure and melatonin administration, the phase of the endogenous rhythm can be delayed or advanced. Administering melatonin in the evening shifts the phase to earlier in the evening, while administering it in the morning causes the phase to be delayed.[11] The opposite is also true for light exposure. Intense light exposure in the evening delays the phase, while light exposure in the early morning advances the phase. Thus, phase changes in circadian rhythm disorders can be regulated through the use of bright light and melatonin at appropriate times.[12]

Initial data from various studies have shown that the eyes are essential for circadian photoreception. Individuals who do not have eyes because of bilateral enucleation or developmental disorders cannot entrain their circadian rhythm to the 24-hour light-dark cycle.[13] The same applies to most individuals whose eyes are preserved but have no light perception due to total blindness. Most legally blind individuals who still have some degree of light perception, even with little functional vision, have normal circadian rhythms.[13]

Blindness and its Effect on Circadian Systems

Definition and Prevalence of Blindness

The legal definition of blindness is having a corrected visual acuity 1/10 of normal (i.e., 20/200) or worse despite correction, or a visual field of 20 degrees or less. People with corrected visual acuity between 20/70 and 20/200 are described as having "low vision."[14,15]

The exact prevalence of blindness is difficult to estimate. According to World Health Organization data for 2000, there were approximately 45 million visually impaired people worldwide. This number was expected to increase by 1-2 million each year to reach 75 million by 2020.[16] The 2010 Global Burden of Disease Study estimated that there were 32.4 million blind individuals.[17] In 2000, it was determined that there were approximately 937,000 blind people in the United States of America (approximate prevalence of 0.78%).[18] It was also estimated in 2000 that approximately 120,000 people in Europe were totally blind. According to a study conducted in 2011 by Boğaziçi University Visually Impaired Technology Laboratory, which is one of the most recent studies conducted in Türkiye, there are approximately 400,000 visually impaired individuals in our country.[16]

Relationship Between Circadian Rhythm and Blindness According to its Timing and Etiology

One of the most curious issues related to blindness and circadian rhythm is how differences in its time of occurrence and underlying cause affect circadian rhythm. Blindness can be classified as congenital or acquired according to when it occurs. Congenital blindness refers to a group of diseases and conditions that occur in childhood or early adolescence (before the age of 16) and which, if left untreated, cause blindness or severe visual impairment that is likely to lead to permanent blindness.[19] Acquired blindness occurs later in life in association with various factors.

The World Health Organization uses two methods to classify blindness and low vision in children. The first method, which is a descriptive classification, refers to the anatomical region most affected. These are grouped as globe (e.g., anophthalmia, microphthalmia), cornea (e.g., corneal scar, keratoconus), lens (e.g., cataract, aphakia), uvea (e.g., aniridia), retina (e.g., retinal dystrophies), optic nerve (e.g., optic nerve atrophy), glaucoma, and conditions in which the eye appears normal (e.g., refractive errors, cortical blindness, amblyopia). The second method, which is an etiological classification, classifies blindness according to the underlying cause. This method uses categories based on the time of onset, which is classified as hereditary (during conception; e.g., genetic diseases, chromosomal abnormalities), intrauterine (during pregnancy; e.g., rubella or thalidomide), perinatal (e.g., retinopathy of prematurity, birth injury, neonatal conjunctivitis/ophthalmic neonatorum), childhood (e.g., vitamin A deficiency disorders, measles, trauma), and unknown (e.g., congenital abnormalities).[20] Acquired blindness can also be classified anatomically as in childhood and may occur due to causes such as cataract, glaucoma, age-related macular degeneration, and diabetic retinopathy.

Ophthalmologists' recognition of impaired circadian rhythms in blind patients is important because an irregular sleep cycle can exacerbate the challenges of life. However, not all individuals with total blindness develop circadian rhythm disorder, and identifying circadian rhythm disorder in blind patients can be complex. It is also extremely important to determine whether the patient has any residual light perception and to obtain a clinical history from the patient. The patient should be asked about unusual sleeping and waking hours, periodic insomnia, and daytime sleepiness.[21]

There are a few studies examining the timing and rate of onset of blindness and the effect of the circadian rhythm on sleep disorder. For example, one study investigated the relationship between sleep disturbance and duration of blindness, rate of vision loss, and type of visual field defect, and no significant correlation was observed. There was also no significant difference between those with congenital blindness and those with acquired blindness.[22] Similarly, Leger et al.[23] determined that sleep difficulties in blind subjects were not associated with factors such as congenital blindness or the number of prosthetic eyes. The etiology and affected anatomical structures are more important than the time of occurrence.

As is known, photic entrainment of circadian rhythms stems from the eye and involves a direct axonal pathway from a small portion of the retinal ganglion cells to the suprachiasmatic nucleus. The remarkable feature of this neural circuit is its apparent independence from conventional retinal phototransduction.[24] In animal studies, mice lacking rods and cones were still able to synchronize their activity to the external lighting cycle, and photic entrainment persisted with undiminished sensitivity, suggesting the presence of a different internal retinal (non-rod or cone) photoreceptor.[25,26]

Different studies have shown that circadian rhythms in blind individuals may be normal, abnormal, or non-entrained. Why does circadian rhythm entrainment differ among these individuals, all of whom have vision loss? One determining factor is an individual's degree of vision loss. In fact, the presence or absence of light perception is more important than the extent of vision loss, as individuals will most likely have a normal circadian rhythm if they have some degree of light perception. In one study, individuals with visual acuity of 3/60 Snellen or better, counting fingers, hand movements, or only light perception were found to have normally entrained and similar rhythms.[21]

Another factor is the etiology of blindness. While normal entrainment of the circadian rhythm cannot occur in pathologies involving ganglion cell damage, the circadian rhythm may be normal in pathologies of the outer retinal photoreceptor layer. In one study, 56% of the participants with eye pathologies suspected of damaging the ganglion cell photoreceptor layer (e.g., retinopathy of prematurity, diabetic retinopathy) were classified as non-entrained or abnormal phase entrained, regardless of vision status. Conversely, 85% of participants with conditions affecting retinal layers other than the retinal ganglion cell layer (e.g., retinitis pigmentosa, other retinal dystrophies, macular degeneration, Leber's congenital amaurosis) were classified as normally entrained, regardless of vision status. Among those with eye pathologies affecting the optic nerve (e.g., glaucoma, optic atrophy), 57% had normally entrained circadian rhythm.[27] However, as in many other studies, several eye pathology categories in this study included a small number of participants ($n<5$). Therefore, it was not possible to associate certain eye pathologies with the type of circadian rhythm. In the categories with more participants ($n>5$), the ocular conditions with the highest proportion of abnormal phase entrainment and/or non-entrainment were enucleation for any reason (67%) and retinopathy of prematurity (57%).[27]

Individuals with anterior segment disease (including diseases affecting the anterior third of the eye, the cornea, iris, ciliary body, and lens) are more likely to have normal circadian rhythm. Association with abnormal circadian rhythm was found to be stronger in patients with total anterior segment pathology compared to other anterior segment pathologies (e.g., albinism, aniridia). However, in individuals with anterior segment pathology that completely obscures posterior segment examination, retinal disease is more likely to be missed and this may be associated with abnormal phase entrainment.[27] In a different study, sleep disturbances were found to be more

common in low vision conditions caused by uveitis compared to other pathologies.[22]

These potential associations warrant further investigation because diseases associated with progressive degeneration in certain areas of the eye may increase the patient's risk of developing a circadian rhythm sleep disorder. Such studies will also be relevant in decision making before elective enucleation if the eyes still have functional light perception.[27] Therefore, studies with more participants are needed to elucidate these potential relationships.

In summary, while studies point to a significant relationship between the etiology of blindness and circadian rhythm disorders, it has been shown that congenital and acquired blindness do not differ in their effect on sleep problems.[23]

Relationship Between Blindness and Circadian Rhythm Sleep-wake Disorders

Total or partial vision loss leads to structural and functional changes in the visual cortex and various other parts of the brain. Numerous studies have demonstrated these changes using neuroimaging techniques and electrophysiological methods. Individuals with total or partial blindness were found to have changes in the cortex and other brain regions because of reduced vision.[28,29] A study by Noebels et al.[30] showed that blind people had reduced resting occipital alpha oscillations when their eyes were closed. Studies by Kriegseis et al.[31] in 2006 and Schubert et al.[32] in 2015 demonstrated decreased parieto-occipital alpha activity indicating changes in the thalamo-cortical pathway in blind people. In addition to such anatomical and physiological changes, the decrease or absence of light input in blind people can also bring about significant changes in circadian rhythm.

There are also limited data on sleep structure and electrophysiological changes in blind people. These limited studies have yielded inconsistent information regarding rapid eye movement (REM) and the non-REM (NREM) stages. Some studies with small samples of blind individuals (n=5) indicated a decrease or absence in deep sleep (N3, formerly NREM stages 3 and 4), characterized by slow sleep wave.[33] These findings were confirmed in another study with a larger sample (n=10).[34] However, none of these studies showed any difference in REM sleep and NREM stage 2 between blind people and those with normal visual function. In a larger study (n=26) by Leger et al.,[23] all of the blind individuals were shown to have free-running circadian rhythms and shorter sleep duration, lower sleep efficiency, shorter REM duration, and longer REM latency compared to healthy controls. A prevalence study also conducted by Leger et al.[35] showed that approximately 83% of blind individuals had at least one sleep problem. Miles[36] reported that 76% of blind people in their study (n=50) had sleep-wake disorder and 40% of those people had a cyclical course of symptoms. In another study of 388 blind individuals, 48.7% of the blind group and 9% of the placebo group reported a sleep disorder.[22] In a study conducted with 794 individuals with blindness in France, 83% of the participants with blindness and 57% of the control group had at least one sleep problem (difficulty falling asleep, disrupted nighttime sleep, waking early in the morning, non-restful sleep, and poor sleep quality), while 18% of the blind group and 8% of the control group met the diagnostic criteria for non-24-hour sleep-wake disorder.[35] In another observational study conducted in New Zealand, there was a high frequency of sleep disorders. In particular, sleep timing problems associated with decreased light input were seen in 55% of blind individuals, while this rate was 4% in the matched general population.[37]

Data from studies conducted with blind individuals are very limited because they were obtained from small samples and generally did not include a circadian marker.[38] However, it is known that most individuals without light stimuli have a circadian rhythm sleep-wake disorder called non-24-hour sleep-wake disorder, also known as free-running sleep phase disorder.[27] Because it is uncommon in the general population, this disorder is inadequately understood and diagnosis is delayed considerably in some cases. Although non-24-hour sleep-wake disorder can be partially explained by decreased light input, it is not yet fully understood what causes other sleep disturbances in blind people.

Non-24-Hour Sleep-Wake Disorder (Free-running Sleep Phase Disorder)

In non-24-hour sleep-wake disorder, which is rare in individuals with normal visual function but common in total blindness, people experience desynchronization of the circadian rhythm because they cannot receive the light input that enables the circadian rhythm to be entrained to a 24-hour period. This results in progressive sleep-wake phase delay, characterized by a progressive delay in sleep onset.[39] In other words, they have a sleep-wake cycle in which nearly every day they fall asleep a few hours later and wake up later than the previous day. As a result, they experience insomnia at night and prolonged daytime sleepiness during the day.[40] In addition to sleep-wake problems, the disrupted circadian release of hormones such as melatonin and cortisol leads to appetite and digestive problems.[41] All of these symptoms are reflected in people's vigilance, mood, and performance during the day, causing disruptions in their social, academic, and professional lives. Most individuals with vision loss report that non-24-hour sleep-wake disorder affects them more than blindness.[41]

According to the International Classification of Sleep Disorders-third edition (ICSD-3), criteria A, B, C, and D are required for the diagnosis of non-24-hour sleep-wake disorder (**Figure 1**).[37]

The high frequency of non-circadian sleep disorders (e.g., insomnia, excessive sleepiness) and clinical manifestations such as depression and anxiety that cause various sleep problems in blind people often make it difficult to establish a diagnosis. In this sense, it is diagnostically valuable to demonstrate the daily shift in the sleep-wake cycle by keeping an actigraphy record for at least 2 weeks, as recommended in the ICSD-3 guideline for the diagnosis of non-24-hour sleep-wake disorder. Actigraphy is a noninvasive, watch-like measurement device worn on the wrist or ankle to measure sleep-wake cycles and motor activity.

This allows periods of rest and movement to be recorded and saved. Biochemical measurements are also recommended when necessary. Analysis of 24-hour urine, saliva, or blood samples two or three times over a period of 2-4 weeks are recommended to measure levels of 6-sulfatoxymelatonin, the main metabolite of melatonin.[42] Urine samples are typically collected every 4 hours during the day and over 8-10 hours at night. In people with non-24-hour sleep-wake disorder, repeated sampling will show abnormal circadian clock periodicity (<23.8 or >24.2 hours) and a gradual shift in the melatonin secretion profile. However, repeated measurement of 6-sulfatoxymelatonin is expensive and should be reserved for individuals at high risk for non-24-hour sleep-wake disorder. Measurement of other biomarkers, such as cortisol, can be used in complex cases or in cases of abnormal melatonin release, such as pineal resection.

Clinical Implications of Circadian Rhythm Disruption Associated with Blindness

Disruption of the circadian rhythm results in desynchronization of internal physiological processes such as cortisol, melatonin, and body temperature regulation, and these recurrent disruptions in the circadian system have negative effects on the endocrine, gastrointestinal, cardiovascular, and reproductive systems, as well as on mood. Alterations in these systems also lead to adverse effects on the immune system and increase the incidence of cancer. For example, the International Agency for Research on Cancer has classified shift work that causes circadian disruption as a possible carcinogen in humans.[43,44] A study by McHill et al.[45] showed that under laboratory conditions, circadian desynchrony led to reduced daily energy consumption and, if not compensated for by increased activity and reduced calorie intake, resulted in weight gain and adverse health outcomes. Circadian disruption due to shift work was reported to disrupt behavioral rhythms such as meal timing and lead to significant cardiac and general health consequences.[46,47] Night shift work has been shown to be associated with increased cardiometabolic disease, metabolic syndrome, type 2 diabetes, and cardiovascular heart disease due to its disruption of circadian synchronization.[48,49,50,51,52,53] Other studies have reported various gastrointestinal complaints and difficulties such as menstrual irregularities, dysmenorrhea, and gestational hypertension.[54,55] Boivin et al.[56] reported that circadian disruption due to shift work led to impairments in cognitive functions and performance. Other studies have also supported that impairment of circadian rhythm will lead to impairment of cognitive functions, severe sleepiness, and attention errors.[57,58]

Disturbances in circadian rhythm and melatonin release are thought to play a role in ocular diseases such as dry eye, corneal wound healing, glaucoma, myopia, cataract, and retinal diseases.[59] Tear osmolarity is known to show a circadian pattern. Inverse to tear volume, tear osmolarity is low in the morning and increases at night as sleep approaches.[60] In sleep-wake disorders associated with impaired circadian rhythm, dry eye disease may develop because the tear production pattern is disrupted. Corneal epithelial healing is also believed to be regulated by a circadian cycle, and mitotic activity peaks in the evening hours.[61] Some experimental studies have indicated that topical melatonin and its derivatives accelerate corneal wound healing.[62] Additionally, aqueous humor production in humans is influenced by circadian rhythm.[63] While the rate of aqueous humor production is high during the day, it decreases at night.[64] The aqueous humor outflow rate is also lower at night than during the day.[65] In glaucoma patients, the disruption of this equilibrium leads to increased intraocular pressure. Melatonin, which plays an important role in regulating circadian rhythm, reduces aqueous humor production. A comparison of melatonin concentrations in the aqueous humor and blood of glaucoma patients and normal individuals revealed significantly higher melatonin levels in the glaucoma patients.[66] Therefore, some studies have linked daytime changes in intraocular pressure to fluctuations in melatonin levels, and it has been suggested that some melatoninergic mechanisms play a role in the circadian rhythm of intraocular pressure.

Considering all of these data, it is apparent that circadian rhythm disturbance is associated with many negative health outcomes. In blind individuals, non-24-hour sleep-wake disorder caused by disrupted circadian alignment may not only lead to disruption in the sleep-wake cycle, but may also cause serious physical and mental conditions. The paucity of literature data on this subject indicates that new studies should be conducted.

Treatment Approaches in Non-24-Hour Sleep-Wake Disorder

Treatment for non-24-hour sleep-wake disorder is effective. People treated with various approaches show synchronization of the circadian rhythm to 24 hours and improvement in symptoms of insomnia and prolonged daytime sleepiness.[67]

Behavioral approaches such as regularizing sleeping, waking, and meal times and physical activity in the morning are recommended as first-line treatment. If partial light perception is present, daytime light exposure or morning bright-light therapy is recommended. Intellectual activities that increase alertness, a cold shower, or intense physical activity in the morning may be beneficial (**Figure 2**).

Pharmaceutical treatment consists of fast- and prolonged-release melatonin preparations and melatonin agonists. As the goal of therapy is to prevent further circadian drift, initiating treatments when the patient is in phase with the solar cycle may be most effective. This may require waiting for the patient's sleeping and waking hours to return to approximately normal, but that is not always possible.

Melatonin has a short half-life of 20-45 minutes because of the first-pass effect in the liver.[68] Given the role of melatonin on circadian rhythms, it is necessary to distinguish its acute sedative effects from its phase regulatory effect, also called the "chronobiotic effect."[69] Exogenous melatonin therapy has an acute sedative effect, a phase regulatory effect, as well as an effect on endogenous circadian rhythms such as body temperature.[70] Its phase regulation activity is related to the timing of administration.[12] Melatonin given early in the evening

advances the circadian clock, leading to earlier sleep onset and waking time, while melatonin given early in the morning leads to later sleep onset and waking time. However, the delaying effect of morning melatonin on circadian rhythm is less potent than the advancing effect of evening melatonin, leading to the risk of napping during the day.[71] Exogenous melatonin given in the late afternoon is often effective in helping patients with delayed sleep phase syndrome fall asleep and wake up earlier, but early morning melatonin has little to no effect in this group of patients.[72] Melatonin given mid-day also has no phase-corrective effect. The effect of melatonin on non-24-hour sleep-wake disorder depends on the person's circadian phase when treatment is started. If the circadian phase is already synchronized or is mildly delayed, evening melatonin administration advances the circadian phase and ensures proper alignment of the circadian rhythm.

In non-24-hour sleep-wake disorder, recommended treatment is 3-5 mg of melatonin at night 1 hour before sleep for the first month, continuing with 0.5 mg for maintenance after synchronization. Melatonin is also widely sold as a dietary supplement in Türkiye and the United States in addition to its sale as a pharmaceutical agent. However, the melatonin preparations sold as supplements are usually well above the dose needed to regulate circadian rhythm. In addition, they are often sold in combination with other preparations such as vitamin B_{12}.[73] Slow-release melatonin preparations are not as effective as normal-release preparations in regulating the circadian rhythm.

Although generally not the first to come to mind in the treatment of circadian rhythm sleep disorders, caffeine has been shown to alter the circadian phase in animals and plant models.[74,75] Caffeine has been shown to delay melatonin release in blind people.[76] In a study including the largest sample of blind individuals with circadian desynchronization, caffeine administration in the morning was reported to be beneficial in alleviating symptoms associated with desynchronized rhythms, such as decreased alertness and low mood, but not effective in regulating circadian rhythm.[77]

Melatonin agonists other than tasimelteon may be useful in regulating circadian rhythm, but these agonists have different pharmacological and pharmacokinetic effects and have not been studied in non-24-hour sleep-wake disorder.

In the SET and RESET studies conducted in 2015, Lockley et al.[78] reported that the melatonin agonist tasimelteon may be effective in the resynchronization of circadian rhythm in people with total blindness. In the first of these two large-scale studies (SET), participants were randomized to receive either 20 mg tasimelteon or a placebo 1 hour before the target sleep time. After approximately 1 month, circadian rhythm synchronization was observed in 8 (20%) of the 40 participants in the tasimelteon group and only 1 (3%) of the 38 participants in the placebo group (17% difference, 95% confidence interval: 3.2-31.6). In the exploratory analysis of 17 patients who continued to use tasimelteon for about 7 months, the rate of circadian rhythm synchrony reached nearly 60%. When tasimelteon treatment was discontinued, patients were observed to return to free-running circadian rhythm. In the RESET study, it was determined that daily use of tasimelteon was necessary to maintain circadian rhythm entrainment, as predicted from the results of the previous study.[78]

Although there are many melatonin agonists, only tasimelteon has been approved by the FDA (United States Food and Drug Administration) and EMA (European Medicines Agency) as a treatment with proven efficacy and safety. Tasimelteon is a potent and specific melatonin 1 (MT1) and 2 (MT2) receptor agonist. It has 2-4 times greater affinity for the MT2 receptor. Its half-life is 1.3 hours and peak plasma concentration is reached between 0.5 and 3 hours after intake. A daily dose of 20 mg in the evening is recommended. Although tasimelteon is well tolerated in the short term, the most common side effects are reported to be headache, elevated liver enzymes, nightmares or abnormal dreams, upper respiratory tract infection, and urinary tract infection. Long-term use has been reported to be safe and well tolerated.[79]

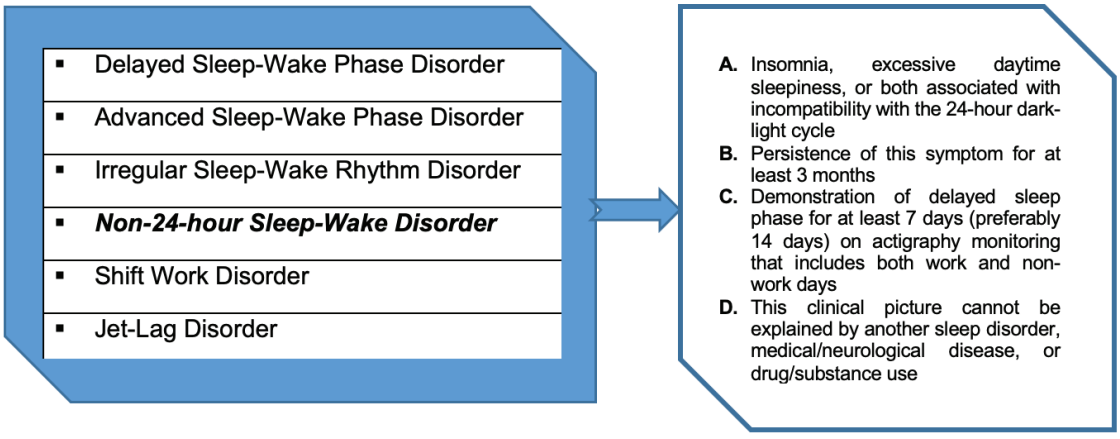

Figure 1. Circadian rhythm sleep-wake disorders (according to the International Classification of Sleep Disorders-3)

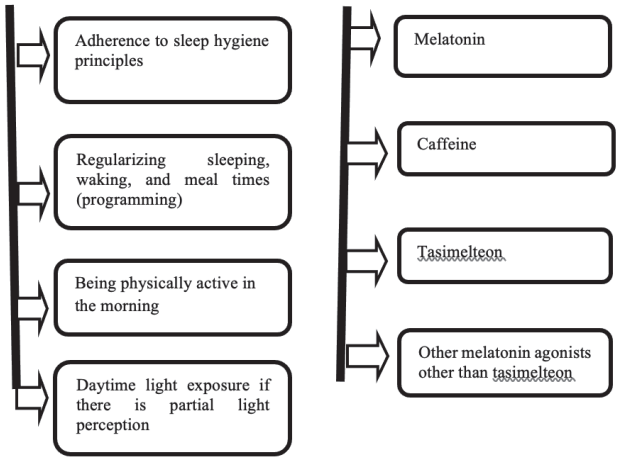

Figure 2. Treatment approaches for non-24-hour sleep-wake disorders

Cost is another important factor in the selection of treatment for circadian rhythm synchronization, as patients need to take the drug daily to maintain this synchronization. The annual cost of using melatonin is approximately $50, while the annual cost of using tasimelteon is around $60,000.[73]

Conclusion

Blind people who cannot receive light input experience symptoms such as insomnia and excessive daytime sleepiness due to disruption of and inability to re-entrain the circadian rhythm. In addition, disruptions in physiological functions and hormone release regulated by the circadian rhythm lead to various adverse consequences in their social, academic, and professional lives. Keeping a sleep diary, obtaining actigraphy measurements, and when necessary, analyzing biochemical parameters are beneficial when diagnosing non-24-hour sleep-wake disorder, which is very rare in the sighted population but common in the blind. Behavioral and pharmacological methods are often effective in the treatment of this disorder. The need to continuously use the drugs that prevent circadian drift is important in terms of considering effectiveness and cost when selecting pharmacological treatment. The diagnosis is often delayed, causing considerable functional losses for blind people, who already face obstacles in many areas of daily life. Diagnosis is also relevant to treatment, as the sleep patterns of blind people can be made more normal through the use of melatonin and its analogues, or phototherapy if they have residual vision. Therefore, assessing sleep problems and planning treatment accordingly for individuals presenting with blindness is an important issue for ophthalmologists to keep in mind.

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