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Original Article

A Review Article on Circadian Rhythm and Effects of Cannabinoids for Sleep-Wake Disorders

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ABSTRACT

Sleep disorders, including circadian rhythm disruptions and sleep-wake cycle abnormalities, significantly impact mental and physical health. These conditions range from insomnia and delayed sleep-phase disorder to advanced sleep-phase disorder, non-24-hour sleep-wake rhythm disorder, and irregular sleep-wake rhythm disorder. The circadian rhythm, which is controlled by the hypothalamic master clock known as the suprachiasmatic nucleus (SCN), is at the heart of many sleep problems. The SCN synchronizes physiological and behavioral processes, such as hormone secretion and body temperature, aligning the body with the 24-hour day. Disruptions in this system, influenced by both internal and external factors, lead to a cascade of health issues, including neurodegenerative diseases, cognitive impairments, and psychological disturbances. Emerging research highlights the role of cannabinoids, particularly cannabidiol (CBD) and tetrahydrocannabinol (THC), in managing these disorders. These compounds interact with the endocannabinoid system, influencing sleep architecture, memory consolidation, and mood regulation. Cannabinoid-based therapies, such as nabilone and other synthetic analogs, have shown promise in treating sleep disorders, especially in alleviating symptoms of posttraumatic stress disorder (PTSD) and restless legs syndrome (RLS). This review delves into the physiological underpinnings of circadian and sleep-wake disorders and evaluates current treatments, including light therapy, melatonin supplementation, and cannabinoid-based interventions. Understanding the intricate balance between sleep, circadian rhythms, and emerging treatments can enhance therapeutic strategies, offering improved quality of life for those affected by these disorders.

Keywords: supra chiasmatic nucleus (SCN), Declarative memory, melatonin, Delayed Sleep-Phase Disorder, Advanced Sleep-Phase Disorder, endocannabinoid system, Randomized controlled trials (RCTs),Cannabis sativa (Marijuana), serotonin (5-hydroxytryptamine, 5-HT), restless legs syndrome (RLS), or Wil-lis Ekbom disease (WED), cognitive behavioral therapy (CBT), posttraumatic stress disorder (PTSD).

INTRODUCTION

The timing, duration, and consolidation of human sleep result largely from the interaction of 2 sleep regulatory systems: the sleep-wake homeostat and the circadian timing system.[1]

The term "circadian timing system" describes the near-24-hour rhythmicity of numerous physiological and behavioral processes, such as hormone secretion, body temperature, urine production, and sleep and wakefulness. Signals from the suprachiasmatic nucleus (SCN), a master pacemaker in the hypothalamus, allow the rhythms of cells within an organ and between the body's organ systems to be coordinated. The SCN synchronizes the body's near-24-hour rhythmic activity with the 24-hour cycle of the outside world, a process known as entrainment, in addition to coordinating the rhythmic activity of the body's cells and organs. Early sleep disturbances and/or sleep disorders, such as insomnia, excessive daytime drowsiness, spontaneous sleep attacks, and REM behavior disorder, are common in patients with neurodegenerative diseases. disorders pertaining to the timing of sleep and waking, they are jet lag disorder, shift-work disorder, non-24-hour sleep-wake rhythm disorder, prolonged sleep-wake phase disorder, advanced sleep-wake phase disorder, and irregular sleep-wake rhythm disorder. Sleep benefits memories. Numerous studies convincingly show that newly acquired memories benefit from a consolidation period filled with sleep [2].

When REM sleep occurs, which is mostly in the second half of the night, the brain's oscillatory activity

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mostly consists of low-amplitude, mixed-frequency oscillations that resemble waking electroencephalogram activity along with rapid eye movements, decreased muscle tone, and hippocampus theta oscillations. Because of this ironic, almost waking, brain activity.

Declarative memory includes both episodic memory (remembering events) and semantic memory (remembering facts). Both the initial retrieval and the encoding of declarative memories are vitally dependent on the integrity of the hippocampus development. According to the active system consolidation hypothesis, spontaneous hippocampus memory reactivation, thalamo-cortical sleep spindles, and slow oscillatory activity during SWS must all work in concert for sleep to have a positive impact on declarative memory.

circadian system:

Circadian rhythms are physiologic and behavioral cycles with a recurring periodicity of approximately 24 hours, generated by the endogenous biological pacemaker, the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus.[3]

The SCN controls the pineal gland's melatonin secretion timing, which starts around two hours before the body's normal sleep period and peaks in the middle of the night. A reliable indicator of circadian phase, melatonin onset measured in a low light environment (DLMO) is utilized in both clinical and research settings to ascertain when the endogenous circadian rhythm occurs. The predominant neurotransmitter in the SCN is +-aminobutyric acid, which is found in almost all SCN neurons. SCN neuropeptides are primarily found in the core or shell nuclei. Vasoactive intestinal polypeptide, gastrin-releasing peptide, and neurons expressing bombesin are highly concentrated in the SCN core. The two main neurochemicals found in the SCN shell are somatostatin and neurophysin.

Both direct (retinohypothalamic) and indirect (retinogeniculate) pathways let the SCN to receive photic information from the retina. The primary photoreceptors for the circadian system are the retina's melanopsin-containing ganglion cells.

Three Per genes (the period homolog 1 gene, Per1; the period homolog 2 gene, Per2; and the period homolog 3 gene, Per3), the circadian locomotor output cycles kaput gene, Clock; the cycle gene, Bmal1; and two plant cryptochrome gene homologs (the cryptochrome 1 gene, Cry1, and the cryptochrome 2 gene, Cry2) make up the core set of clock genes that genetically determine circadian rhythms. The molecular underpinnings of circadian rhythmicity are provided by transcription-translation feedback loops that are formed by the interaction of these genes and their products. The Per and Cry genes' transcription is activated by Clock's interaction with BMal1 during the day, leading to elevated amounts of these transcripts. All Circadadian rhythm sleep disorders are diagnosed using an actigraphy-based sleep diary and a thorough medical history. It is not usually recommended to use polysomnography (PSG) to confirm the diagnosis. PSG is recommended, nevertheless, in order to screen for further concomitant sleep disorders. Patients with almost all forms of CIRCADIAN RHYTHM SLEEP problems also frequently have psychiatric problems, including anxiety and depression, which should be taken into account in the differential diagnosis in addition to concomitant sleep disorders.

Delayed Sleep-Phase Disorder:

The severity and population categories surveyed determine the prevalence of Delayed Sleep-Phase Disorder, which ranges from 0.2% to 10.0%. Adolescents and young adults are more likely to experience milder instances. Although there doesn't seem to be any sex preference, males experience phase delay later than females in adolescence, peaking at age 21 and 17, respectively. According to the International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual, patients with Delayed Sleep-Phase Disorder often go to sleep between 1:00 AM and 6:00 AM and wake up in the late morning to early afternoon. There is also a familial propensity for Delayed Sleep-Phase Disorder.

Advanced Sleep-Phase Disorder:

The main treatments for Advanced Sleep-Phase Disorder, according to the AASM practice standard, are timed light exposure and sleep-wake timing. Timed light exposure in the evening and avoiding light in the early morning are two useful therapy strategies for ADHD. For insomnia related to sleep maintenance, melatonin or hypnotics may be helpful. When bright light is given prior to the body's core temperature dropping, it can effectively postpone the circadian phase. Early-evening light therapy, often administered between 7:00 and 9:00 PM, is the most

widely utilized treatment for Advanced Sleep-Phase Disorder.

Sleep is an essential physiologic function that alternates with wakefulness[4].

erratic eye movements Neurons in the pons, hypothalamus, and non-random eye movement control sleep. Neurons in the preoptic regions (such as the ventrolateral preoptic nucleus) that block the ascending arousal systems control sleep. Gamma-aminobutyric acid (GABA) and galanin are two examples of inhibitory neurotransmitters that largely control these sleep-promoting areas. Cholinergic neurons found in the dorsolateral pons also support and sustain REM sleep. Neurons in the reticular formation, particularly the rostral half, are the main mediators of wakefulness. Sections of the thalamus, hypothalamus, and forebrain receive excitatory projections from these neurons. The main neurotransmitters involved in promoting wakefulness include cholinergic, monoaminergic, and orexin/hypocretin.

endocannabinoid system:

Cannabinoid receptors and endogenous lipid ligands make up the majority of the endocannabinoid system. Eicosanoids, anandamide (N-arachidonoylethanolamide), and 2-arachidonoyl glycerol (2-AG) are examples of endogenous ligands. These (as well as exogenous substances) influence the CB1 and CB2 cannabinoid receptor types. While CB2 receptors are mostly peripheral (found in the immune system, lung, and liver, with the exception of those in the brainstem), CB1 receptors are mainly central (found in the thalamus, hypothalamus, cortex, hippocampus, limbic system, and basal ganglia). It has been proposed that sleep induction may include CB1 receptors found in the pons and basal forebrain. This process may be connected to the activation of cholinergic neurons that help induce sleep and are found in the pons and basal forebrain via CB1 receptors. Modulation of the sleep-wake cycle is another function of the serotonergic transmitter system, which is found in the brainstem's dorsal raphe nucleus.

Histamine, noradrenaline, orexin/hypocretin, and other arousal systems provide afferent inputs to these serotonergic neurons.

cannabis withdrawal :

Vibrant dreams and sleep problems are linked to cannabis withdrawal. Prior heavy marijuana users showed reduced total sleep duration (TST), decreased SWS, and decreased REM latency as compared to controls in a research evaluating several PSG parameters. Although the study was constrained by the absence of baseline PSG data in both groups, this group likewise showed a longer sleep start and lower sleep efficiency than the control group. Another study found that abruptly stopping extensive marijuana usage was associated with an increase in periodic limb movements (PLMs).Heavy users have been reported to experience more severe withdrawal-related sleep problems, which typically start 24 to 72 hours after stopping and last for up to 6 to 7 weeks. Considering these varying impacts on sleep architecture that are based on duration. The reward mechanism controlling food intake and, in particular, hedonic feeding—excessive food intake in relation to energy requirements—are both regulated by the endocannabinoid system. Particularly in obese people, endocannabinoid activity may be out of sync with the central circadian rhythm, which is linked to weight gain and a stated preference for eating later.

Randomized controlled trials (RCTs) have recently begun to assess the impact of several cannabinoid medicines on chronic insomnia. These include the use of CBD alone or different combinations of CBD, THC, and cannabinol (CBN). A proof-of-concept study evaluating the safety and effectiveness of a single dose of ETC120 oil, a product containing THC and CBD, in patients with chronic insomnia is one of these proposed trials, the CANSLEEP trial (cannabidiol and Δ9-tetrahydrocannabinol for chronic insomnia disorder). It is based on PSG data, EEG, and source modeling (using brain MRI).

Cannabinoids:

Cannabis sativa (Marijuana) has a long history as a medicinal plant and Δ9-tetrahydrocannabinol (Δ9THC) is the most active component in this plant.[5] The Cannabis Sativa plant, also known as marijuana, naturally contains cannabinoids, with Δ9-tetrahydrocannabinol (Δ9-THC) being the most potent of these compounds. On the one hand, cannabinoids have the potential to cause a wide range of negative side effects, including dizziness, dyspnea, diarrhea, constipation, pneumonia, abdominal pain, renal diseases, and mental health issues. They can also significantly impair cognitive abilities including memory and learning. Conversely, a variety of conditions can be treated with cannabinoids,

including epilepsy, multiple sclerosis or spinal cord injury-related spasticity, irritable bowel syndrome, anorexia and weight loss, chronic pain, chemotherapy-induced nausea and vomiting, Amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease, anxiety and depression, posttraumatic stress disorder (PTSD), and sleep disorders.

Serotonin:

The midbrain and raphe nuclei of the brainstem produce the wide-projecting modulatory neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). One significant neurotransmitter that is essential for regulating the sleep-wake cycle is serotonin. One of the first neurotransmitters linked to the physiology of the sleep-wake cycle was serotonin. Additionally, the first identified sleep-promoting chemical in the field of sleep neurology is serotonin. It has been demonstrated that serotonin regulates the sleep-wake cycle by influencing different receptors, depending on where it is located in the brain and what kind of receptor it interacts with.

Clinical and preclinical studies describe a circadian rhythm in circulating endocannabinoid concentrations ,with plasma 2-AG levels increasing from mid-sleep to early afternoon in humans; an effect amplified by sleep restriction [6].

With minimal impact on NREM sleep, CBD microinjected into the amygdala's central nucleus corrected stress-induced REM suppression in an animal model of sleep disorders brought on by repeated exposure to anxiety-inducing situations. This suggests that sleep can be improved by an anxiolytic mechanism that is yet unclear but may entail activation of the serotonin 1A (5-HT 1A) receptor and/or augmentation of AEA signaling through inhibition of FAAH and FABPs. Additional preclinical data indicates that endocannabinoids, ole-amide and 2-AG, which activate the CB1 receptor, normalized the sleep disorders associated with maternal separation, including increased alertness and a reduction in the length of NREM and REM sleep. Additional preclinical data indicates that endocannabinoids might possibly be involved in regulating the production of REM sleep in rats after sleep loss.

An increasing body of research suggests that nabilone, a synthetic THC analog, may be useful in treating PTSD patients' nightmares. Nabilone (0.5 mg/d up to a maximum of 3 mg/d) significantly decreased the incidence of nightmares in both an RCT and an open-label research. Half of the participants experienced mild side effects, with headache, dizziness, and dry mouth being the most prevalent.

Even at extremely large dosages (such as 1500 mg twice daily for six days or 6000 mg as an acute dose), CBD is non-intoxicating and has been demonstrated to be safe and well-tolerated in people. In healthy volunteers, abruptly stopping a 4-week course of 750 mg CBD twice daily did not result in any signs of withdrawal symptoms. The cytochrome P450 enzyme pathways, which are involved in the biotransformation of numerous frequently prescribed drugs, are strongly substrateed and inhibited by THC and CBD.As demonstrated recently between CBD and the anticonvulsant medication clobazam in children with severe epilepsy, potential drug-drug interactions with cannabinoids are theoretically possible.

In 2000, the American Academy of Sleep Medicine officially recognized sleep disorders associated with pregnancy as a separate entity defined as the occurrence of insomnia or excessive daytime sleepiness in the course of pregnancy.[7]

pregnancy-related sleep disturbances:

Sleep disturbance can be caused by a variety of pregnancy-related issues. According to one study, heartburn has been documented in up to 75% of pregnancies, making it far more common during pregnancy. The hormone that causes uterine contractions, oxytocin, is known to peak at night, which may contribute to sleep disturbances in the latter stages of pregnancy.

A typical occurrence throughout the first and third trimesters is nocturia. An increase in salt secretion throughout the night is linked to nocturia, which raises urine output during the night. The expanding uterus's impact on bladder capacity in late pregnancy exacerbates nocturia. Sleep disruption can be caused by fetal movements, and sleep fragmentation can also be caused by musculoskeletal discomfort associated with pregnancy-related musculoskeletal changes.

Pregnancy-related physiological changes increase the risk of sleep-disordered breathing. Predisposing conditions include nasal congestion, upper airway edema, elevated Mallampati score, and lower functional residual capacity, all of which lead to

decreased airway patency and increased collapsibility.

restless legs syndrome (RLS):

The sensorimotor phenomenon known as restless legs syndrome (RLS), or Wil-lis Ekbom disease (WED), is typified by an urge to move the legs due to an unpleasant sensation; the urge is more intense during rest or inactivity and is partially or completely alleviated by movement, and the sensation is worse at night or in the evening. The majority of individuals with RLS/WED exhibit periodic limb movements and arousals on polysomnography, even though a sleep study is not necessary to diagnose the condition.

In a research that involved in-person interviews with expectant mothers at delivery, about 25% of the women satisfied the International Restless Legs Syndrome research Group criteria for RLS. About one-third of these women had symptoms prior to pregnancy, whereas nearly two-thirds had symptoms that had just started. It appears that the prevalence of RLS rises with gestational age, indicating de novo symptoms . Symptoms usually go away for most women soon after delivery.

RLS is believed to be caused by malfunctioning of hypothalamic dopaminergic cells, which are the source of spinal dopamine, and has been connected to dopamine metabolism in the brain. Reduced serum iron inhibits the central nervous system's tyrosine hydroxylase production, which in turn inhibits dopamine generation. The three to fourfold increase in iron needs during pregnancy could be one of the possible causes of the greater occurrence of RLS during pregnancy. Since the mother provides the baby with all of its nutrition, the placenta increases its iron transfer systems to ensure that the fetus receives an appropriate quantity, frequently at the price of the mother's stockpiles. When maternal iron insufficiency is present, this increase is more noticeable.

cognitive behavioral therapy (CBT):

In the nonpregnant population, cognitive behavioral therapy (CBT) is advised for the treatment of insomnia. There is a dearth of information regarding CBT use during pregnancy. According to one recent study, women with depression and insomnia who received cognitive behavioral therapy for their insomnia showed improvements in their mood and sleep metrics.

Many medications are avoided during pregnancy due to concerns about teratogenicity.

A rare clinical disease of excessive daytime drowsiness, narcolepsy can also include cataplexy, hypnagogic hallucinations, and sleep paralysis. Cataplexy may coexist with narcolepsy. According to estimates of the US population, it affects roughly 1 in 3000 people. Women with narcolepsy are likely to experience pregnancy complications due to the illness, as it peaks in adolescence and the early 20s.

The cannabis flower is comprised of over 100 different cannabinoids, the active compounds found within the cannabis plant.[8]

cannabis-based medicines:

The potential medicinal influence has led to the development of extracts from cannabis-based medicines. These extracts, which are taken orally, include synthetic THC (dronabinol, nabilone), CBD (Charlotte's web), and nabiximols (1:1 CBD/THC, Sativex). It has been demonstrated that the dosage of CBD administration affects sleep differently. It is true that while high-dose CBD has a sedative impact, low-dose CBD has a stimulating effect. While low-dose CBD has been linked to increased wakefulness, results from a research conducted among people with insomnia indicated that administering 160 mg of CBD daily enhanced total sleep time and decreased the number of arousals during the night. Dissatisfaction with the amount or quality of sleep linked to trouble falling asleep, trouble staying asleep through the night, and/or waking up early in the morning with no way to go back to sleep that significantly impairs functioning or causes distress is known as insomnia. Overall, the prevalence of insomnia has risen recently, rising from 17.5% in 2002 to 19.2% of US adults, or 46.2 million people.

obstructive sleep apnea (OSA):

In the United States, 9% of adult Americans suffer with obstructive sleep apnea (OSA), the most common type of sleep disordered breathing. The standard treatment for OSA involves using a continuous positive airway pressure (CPAP) machine, a mechanical device that maintains the airway open for unforced breathing. Despite the fact that CPAP machines are a successful treatment for OSA, many patients refuse to use them because they are uncomfortable. Numerous research investigations on humans and animals have looked into cannabinoids as possible therapeutic substitutes for the treatment of OSA. A parasomnia known as REM sleep behavior disorder (RBD) causes people to lose their muscle

stiffness during REM sleep, which can lead to nightmares and the potential to act out dream-related activities.

Post traumatic stress disorder (PTSD) related dreams:

Despite advancements in other areas, nightmares linked to posttraumatic stress disorder (PTSD) are frequently a lingering symptom that is challenging to cure. The only medication now available to treat nightmares associated with PTSD is prazozin, an alpha-adrenergic blocker. Nonetheless, a growing number of combat veterans are turning to cannabis to alleviate PTSD symptoms, such as nightmares. This has spurred preliminary studies to investigate how cannabis affect nightmares. Fraser reported on a study that looked at how nabilone, a synthetic version of THC, might help those with PTSD-related dreams. The scientists discovered that nabilone medication enhanced participants' number of hours of sleep per night while decreasing the frequency and severity of nightmares.According to additional studies with a brief follow-up, nabilone has been well tolerated and has been shown to lessen nightmares in male prisoners and military service personnel . Last but not least, an open-label pilot research looking into the use of THC to treat PTSD discovered that it improved sleep quality and decreased the frequency of nightmares. However, some people experienced moderate side effects as headaches, dizziness, and dry mouth.

There is a continuously growing body of evidence pointing out the importance of detecting and consequently assessing sleep disorders in children, resulting from the bimodal association between sleep and neurodevelopment, cognition, and behavior.[9]

Sleep-onset association disorder (SOAD) and limit-setting sleep disorder: are the two main categories of behavioral insomnia in children, which primarily manifests as behavioral features (also known as behavioral insomnias of childhood [BIC]). A third subtype of behavioral insomnia is a combination of the two types. When a child need particular environments or items (such as a pacifier) to fall asleep or stay asleep after being awakened, this is known as SOAD. The BIC limit-setting type is characterized by delayed sleep onset, with or without awakenings, and is brought on by parents who set incorrect boundaries. The kid may refuse to go to bed or constantly request attention (for example, to use the restroom or for a drink). While melatonin has been demonstrated to be helpful in treating other developmental diseases like Angelman syndrome and fragile X syndrome, it has primarily been utilized to treat sleeplessness in the setting of autism spectrum disorder and ADHD. The pineal gland secretes melatonin, a hormone that promotes sleep, at its highest level between two and four in the morning. It affects the number of awakenings and the sleep-onset delay (Economou et al.). Although it has also been suggested that melatonin be taken nine to ten hours after the child wakes up, the recommended dosage is 0.05 mg/kg taken one to two hours before bedtime.

Insomnia is frequently treated with antihistaminergic medications, such as diphenhydramine, promethazine, and hydroxyzine. One of the primary neurotransmitters that promotes wakefulness is histamine. Anti-histaminergic medications work by inhibiting histamine H1 receptors, which promotes sleep by lowering wakefulness and sleep-onset latency but also has the potential to sedate users. The main adverse effect of these medications is sedation, which might persist until the next morning, along with lightheadedness. There may also be anticholinergic adverse effects, such as tachycardia, dry mouth, impaired vision, constipation, and urine retention.

Despite being widely used to treat adult insomnia, benzodiazepines and their hypnotics (such as estazolam and triazo-lam) that operate on gamma-aminobutyric acid (GABA) receptors are rarely administered to children. In addition to having no indication in children,non benzodiazepines (zolpidem, zaleplon) should not be used in children younger than twelve. However, they are utilized as off-label hypnotic medications at bedtime doses of 5 mg or 0.25 mg/kg (for zolpidem) due to their minimal side effects. The issue begins with an overview of the central disorders of hypersomnolence, including narcolepsy, idiopathic hypersomnia and other hypersomnia disorders, and the related use of the entire broad range of stimulant and wake promoting pharmacotherapies. [10]

REM sleep behavior disorder:

An exceptional opportunity to use promising agents and slow the progression of these chronic neurodegenerative disorders has arisen since REM sleep behavior disorder was identified as the most significant prodromal manifestation of disorders linked to synuclein-specific neurodegeneration, including Parkinson disease and dementia with Lewy

bodies . With Drs. Jeffrey Hall, Michael Rosbash, and Michael Young winning the 2017 Nobel Prize in Medicine or Physiology, the circadian system and its underlying biological principles—which play a critical role in physiological and behavioral homeostasis—received wider, long-overdue recognition. For the treatment of insomnia and hypersomnias, pharmacotherapies with new wrinkles in their proposed mechanisms of action are now available. These include pitolisant, a novel histaminergic wake-promoting agent, and lemborexant and suvorexant, which work by antagonistically interacting with hypocretin to induce sleep. The availability of "smarter," auto-titrating positive airway pressure devices has also significantly improved the management of sleep-related breathing disorders by providing patients and practitioners with significantly better analytics and remote monitoring capabilities to better measure treatment outcomes, increase access for monitoring larger patient populations, and improve patient tolerability. The term “circadian” is derived from the Latin circa dies, which means around a day. [11]

The CTS controls the timing of the sleep-wake cycle, which is normally synced with nighttime in most people. Through direct and indirect projections to brain areas related to arousal and sleep, the SCN helps regulate the timing of sleep. Thus, the homeostatic sleep pressure (process S), which increases with the amount of time spent awake, interacts with circadian cycles in alertness, sleepiness, mood, and other behaviors (process C).

The International Classification of Sleep Disorders, Third Edition (ICSD-3) defines CRSWDs as recurring or persistent patterns of sleep disturbance that are mainly caused by one of the following: a misalignment between the endogenous circadian rhythm and exogenous factors that impact the timing or duration of sleep, or changes to the circadian rhythm system.

One effective pharmaceutical strategy for treating CRSWDs is to target the melatonin receptors in order to change and stabilize the circadian phase. The pineal gland's production of melatonin is thought to be a consistent and dependable indicator of the circadian phase of the central pacemaker, which is regulated by a multisynaptic route that starts in the SCN. Through feedback to melatonin receptors in the SCN, the duration of melatonin secretion in healthy individuals is believed to reciprocally influence the circadian clock and accurately reflect the duration of darkness. Treatment of circadian rhythm sleep disorders are based on timed bright or blue light (morning for delayed and afternoon for advanced phase disorders) and melatonin (1 hour prior to required bedtime in delayed phase disorder) [12].

Tasimelteon: has recently been discovered to be beneficial for blind individuals with non-24-hour sleep-wake phase disorder. It is also beneficial to advise patients that the outcome of treatment for delayed sleep-wake phase disorder may depend on how precisely any therapies are timed. For instance, the impact of light is contingent upon the wavelength and spectrum of the light, intensity, previous exposure to light, and—above all—timing.

obstructive sleep apnea:

Conservative treatments for obstructive sleep apnea, like losing weight and avoiding the supine posture (for positional sleep apnea), may be beneficial. Positive airway pressure therapy is currently the most popular and first-line treatment for obstructive sleep apnea. Bilevel therapy produces a higher pressure during inspiration and a lower level during expiration, whereas continuous positive airway pressure involves a constant flow of air into the nose. Higher demands can occasionally make the latter more at ease. Treatment has been accelerated thanks to auto-titrating devices.

Complex sleep apnea can also be treated using adaptive servo-ventilation. Additionally, it can enhance glucose regulation and blood pressure. For patients who are resistant of positive airway pressure therapy or who have mild to moderate cases of obstructive sleep apnea without any significant risk factors, oral devices such mandibular advancement devices may also be helpful. The most popular surgical therapy options are maxillo-mandibular, nasal, and soft palate surgeries.

Central hypersomnia: is rarely caused by disorders. These include idiopathic hypersomnia (long sleep duration or no sleep duration), recurrent hypersomnia (like Kleine-Levin syndrome), narcolepsy type 1 (cataplexy), and narcolepsy type 2 (no cataplexy). One disorder that affects the regulation of rapid eye movement sleep is narcolepsy. Sleepiness, sleep paralysis, and hypnagogic hallucinations are examples of classic symptoms. In narcolepsy type 1, cataplexy is characterized by a decrease of muscular

tone that is usually triggered by pleasant feelings, such as laughing or telling a joke. Anger or astonishment can occasionally act as a trigger. Traditionally, naps during the day are brief (15–40 minutes) and rejuvenating for those with narcolepsy. Patients with narcolepsy type 1 may also have reduced levels of orexin in their CSF fluid, which is associated with a common genetic connection (DQB1*0602 haplotype).

Modafinil or armodafinil are usually the first medications used to treat drowsiness. Stimulants like methylphenidate or amphetamine/dextroamphetamine can be utilized if these are not tolerated or don't work. Blood pressure monitoring and an evaluation for arrhythmias, which these drugs can exacerbate, should be precautions. For usage during pregnancy, none of these have received approval. Cataplexy reacts to sodium oxybate or antidepressants, usually selective serotonin reuptake inhibitors (SSRIs). Up to 10% of narcolepsy patients have rapid eye movement behavior disorder, which is a common comorbidity of narcolepsy, along with periodic limb movement during sleep.

serum ferritin in pediatric RLS:

The term “sleep-disordered breathing” describes the clinical spectrum which includes snoring, upper airway resistance syndrome (UARS) and obstructive hypopnea syndrome. [13]

Since children have trouble expressing their symptoms and caretakers find it difficult to identify them, pediatric RLS may be challenging to diagnose. For the diagnosis of definitive instances of childhood RLS, there are consensus criteria tailored to pediatrics; more criteria are available for research and probable cases. In adult research, serum ferritin levels below 50 mcg/L have been linked to the severity of RLS, and in children, this has been suggested as a cause. Although no comprehensive studies have been conducted, there is some indication that at least some children with RLS have low iron storage (ferritin < 50 mcg/L in 83–89% and fewer than the median for age and gender in 72–75%). Given that serum ferritin levels below 50 mcg/L are more prevalent in children than in adults, some have suggested that low iron storage may be more significant in children than in adults.

A good strategy is to take 3 mg/kg/day of elemental iron orally, with vitamin C, on an empty stomach, and without concurrent consumption of calcium-containing foods or beverages. A ferritin test should be performed two to three months after therapy starts. RLS/PLMD symptoms may be exacerbated by caffeine, nicotine, and drugs including over-the-counter antihistamines and prescription drugs like metoclopamide, tricyclic antidepressants, selective serotonin reuptake inhibitors, and antidopaminergic medicines. Stimulant medicines have not been shown to exacerbate RLS/PLMD symptoms in people with concurrent ADHD, provided that the stimulant effect wears off before evening.

Gabapentin: an FDA-approved anticonvulsant for children older than three, is another drug that has been used off-label to treat childhood RLS. It may help with sensory disturbance in RLS. Enacarbil, gabapentin's longer-acting counterpart, has been investigated in adults and was just put on the market. With limited evidence, benzodiazepines, opiates, and clonidine, an antiadrenergic antihypertensive occasionally recommended for treating children's sleep onset issues, have all been reported or recommended for treatment in pediatric RLS. Consideration should be given to the potential cardiovascular effects of clonidine as well as the daytime sedation brought on by gabapentin and benzodiazepines. Circadian rhythms have been observed to affect a wide variety of endocrine functions, gastric acid secretion, motor activity pattern, breathing, blood pressure, as well as both normal and abnormal central nervous system activity. [14] The hypothalamic suprachiasmatic nucleus, which gets information from the direct retinohypothalamic route, controls how circadian rhythm affects sleep. Hypothalamic synchronization of internal circadian rhythms with extrinsic conditions facilitates regular entrainment of the body with the external environment. Through the retinohypothalamic pathway, light activation of retinal ganglion cells—which are different from rod and cone cells—is transmitted directly to the hypothalamic suprachiasmatic nucleus, which in turn controls a number of physiological processes, such as metabolism, autonomic and endocrine function, and cardiac rhythm.

Melatonin: regulates the expression of several genes, such as PER1, PER2, and BMAL1, which have been linked to circadian rhythm functions. Numerous studies have documented circadian rhythm disruption in dementia patients. Individuals with

dementia who have known circadian rhythm abnormalities also exhibit changed patterns of motor activity. This could be because midline brain areas important in circadian regulation are experiencing increasing neurodegeneration. According to a recent study, autopsy data point to a loss of melanopsin cells and a decrease in the thickness of the retinal nerve fibers. The suprachiasmatic nucleus may also be affected by neurodegeneration, leading to sleep fragmentation and a delay in the circadian rhythm.

A sleep-wake rhythm disorder that interferes with a patient's normal entrainment and synchronization to a 24-hour circadian rhythm is known as non-24-hour sleep-wake disorder. The underlying cause of non-24-hour sleep-wake disorder is that most people's intrinsic biological circadian period duration is closer to 24.2 hours, which is longer than 24 hours. Entrainment to the shorter 24-hour clock day length occurs in normal persons because the hypothalamus is able to synchronize the individual's internal time period due to the high zeitgeber of light input to the suprachiasmatic nucleus.

A clinical subtype of older persons with Alzheimer's disease who suffer sundowning may have lower circadian rhythm amplitude and more severe sleep fragmentation than those who do not.

CONCLUSION

In conclusion, sleep disorders, especially those related to circadian rhythm disturbances, present a complex interplay between biological, environmental, and lifestyle factors. The suprachiasmatic nucleus (SCN) remains central to understanding and addressing these disruptions. Treatment approaches have evolved from traditional therapies, such as light exposure and melatonin regulation, to innovative cannabinoid-based treatments, which have shown efficacy in managing specific disorders. Cannabinoids, like CBD and THC, have emerged as promising agents, impacting not only sleep quality but also addressing co-occurring issues like anxiety, PTSD, and neurodegenerative conditions. For example, randomized controlled trials indicate that nabilone can significantly alleviate PTSD-related nightmares, while CBD may regulate REM sleep disturbances and enhance non-REM sleep quality.

Nonetheless, further research is essential to refine dosing, long-term efficacy, and safety, especially given the complex nature of cannabinoid interactions within the endocannabinoid and circadian systems. Also, the increasing prevalence of sleep disorders across age groups and its link to lifestyle factors underscore the need for personalized and integrated approaches. These findings highlight the potential of combining pharmacological and behavioral interventions to restore circadian alignment and improve sleep health. As the understanding of sleep disorders deepens, a tailored, multifaceted therapeutic approach could redefine treatment, providing sustainable relief and enhancing overall well-being.

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