

Comprehensive Overview on Sleep

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ABSTRACT

The circadian rhythm mediated by the suprachiasmatic nucleus of the hypothalamus is primarily responsible for maintaining the sleep and wakefulness states. Numerous physiologic mechanisms and bodily repairs occur during the state of sleep along with functional alterations in both the autonomic and somatic nervous systems. Most individuals cycle through three stages of nonrapid eye movement sleep, accounting for about 75% of total sleep duration, followed by rapid eye movement sleep, which makes up the remaining 25%. Besides the above, endocrine factors like the release of melatonin from the pineal gland also have a significant impact on the initiation and maintenance of sleep phases. The emotional factors and the limbic system in association with a multitude of variables like stress, drugs, substance use like alcohol, appetite, and behavioral patterns are known to modulate a typical sleep cycle. Given below is a detailed review of normal sleep physiology and numerous sleep-related disorders, their risk factors along with their management, and a brief description of all factors that influence as well as alter the neuronal signaling processes of the brain.

Keywords: Circadian rhythm, Melatonin, Review, Risk factors, Sleep, Sleep disorders.

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INTRODUCTION

Sleep is a complex yet dynamic process that plays a pivotal role in many biological activities that occur in the body. It is heavily regulated by numerous different variables that have the potential to alter not only the depth, and duration but also the quality of the sleep stages.

The genetic preponderance for many aspects of the sleep cycle and their associated dysregulation induced by independent unidentified factors are still under close study. Some new elements are explored each day and the contribution towards sleep pathologies is being established. Nevertheless, it is still said that many grey areas that when uncovered can create links between different bodily processes that integratively act and balance the sleep function.

SLEEP PHYSIOLOGY

The sleep cycle is composed of two main processes: the nonrapid eye movement stage (NREM) and the rapid eye movement stage (REM).¹ Both NREM and REM alternate with each other throughout our time spent asleep. Nonrapid eye movement stage can be divided into four stages that eventually lead up to REM sleep, thus, 75–80% of our sleep is in the NREM state and only 20–25% is in the REM state. Each stage of NREM holds its function.¹

The 1st stage of NREM consists of alpha waves, associated with alertness and wakefulness. Alpha waves have a frequency of eight cycles per second. This stage of NREM is considered “light sleep”, easily disrupted by external stimuli.¹

The 2nd stage of NREM is the step in the cycle where ~50% of total sleep occurs. This is considered “heavy sleep”, in which sleep spindles and K complexes are formed. The role of the 2nd stage is memory consolidation, the act of solidifying the actions of the day into memory. The 3rd and 4th stages of NREM are known as slow-wave sleep, with a high threshold of arousal.¹

The REM sleep stage is associated with REM, dreaming, and muscle inhibition. This combination allows for the sensation of

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being active in one’s dream without putting the physical body in danger. The REM stage consists of de-synchronized and low-voltage waves.¹

Physiological Changes in Other Systems during Sleep

The autonomic nervous system plays a role in the regulation of homeostasis while we are asleep. There is the regulation of the cardiovascular, respiratory, renal, and endocrine systems, all occurring simultaneously while the sleep cycle is active.¹

The cardiovascular system helps to regulate blood pressure and heart rate depending on what stage of the sleep cycle you are in. Both heart rate and blood pressure increase during the 1st and 2nd stages of NREM. Cerebellar blood flow and metabolism are also reduced during the NREM stage of the sleep cycle, while an increase in cerebellar blood flow is noted with the limbic system and visual association.¹

The respiratory system also fluctuates depending on what stage of the sleep cycle someone is in. Hyperventilation is noted with REM sleep, in which air flow and ventilation are fast, while hypoventilation is noted with NREM sleep, with markedly decreased rib cage movement and decreased activity of accessory respiratory muscle such as pharyngeal and intercostal muscles. It is important to note that physiologic changes in airflow and breathing are least sensed during the 3rd and 4th stages of NREM.¹

The renal system is active during the sleep cycle to modify urine concentration, renal blood flow, and glomerular filtration during the sleep cycle. This overall will help with urine retention during sleep and decrease the urge to urinate while sleeping when functioning.¹

Most importantly, the endocrine system is active throughout the sleep cycle to regulate homeostasis with the release of key regulatory hormones such as growth hormone, thyroid hormone, and melatonin. Growth hormone is released during the 3rd stage of NREM and inhibited by stress, whereas thyroid hormone is released with deep sleep. Melatonin is important in regulating the circadian rhythm and is regulated by the light–dark cycle.¹

Sleep and Immune System

It was found that sleep has a prime role by exerting a regulatory effect on the immune system of our body. It does so by increasing the number of naive undifferentiated T cells and proinflammatory cytokines at nighttime and increasing anti-inflammatory cytokines and cytotoxic cells during the day.²

Sleep also selectively has a role in the formation of immunological memory, especially during slow-wave sleep. High levels of growth hormone, prolactin, and low cortisol and catecholamine concentrations during sleep are responsible for creating a pro-inflammatory state in the body. These changes, in turn, are responsible for generating adaptive immune responses in several lymph nodes. These hormones have a synergistic action on the immune system and help in immune cell proliferation, differentiation, and activation. The waking period is associated with the accumulation of oxidative stress that stimulates a proinflammatory state in the body, which in turn provides positive feedback and supports the initiation of an adaptive immune response.^{2–4}

This boost in immune activation during sleep by the synergistic action of neuroendocrine factors and intrinsic clock genes that maintain circadian rhythm has a beneficial role in maintaining immune responses.

Sleep and Endocrine

Several hormonal changes occur during sleep that serves a role in growth and repair. Growth hormone is responsible for sparing the catabolism of glucose and proteins by inducing lipolysis and causing insulin resistance. It is secreted during the first few hours of the onset of sleep. A state of low-glucose turnover is maintained throughout the sleep cycle, and the hypothalamic–pituitary axis is suppressed during sleep.

It is this growth hormone-induced insulin resistance that is responsible for early morning hyperglycemia, described as the dawn phenomenon. It was also demonstrated that any

malalignment in the circadian rhythm resulted in elevated insulin resistance and high blood pressure.⁵

Studies also showed that alteration in the duration of sleep had a direct impact on the homeostasis of glucose as sleep deprivation caused reduced postprandial insulin secretion.

Thyroid-stimulating hormone and testosterone levels were also found to decrease because of sleep deprivation. These changes mentioned above major insulin resistance development and fluctuations in adipokine production from adipocytes. In addition to this, increased caloric intake and appetite due to sleep restriction contributed to the development of obesity.

It was found that appetite was elevated due to appetite-suppressing peptide YY levels getting lowered because of sleep disruptions and reduction in the levels of leptin with a parallel increase in the levels of ghrelin. These changes promote a diabetogenic profile in the individuals, hence putting them at risk of impaired glucose tolerance.

Sleep and Appetite

At the level of the cortex, there are several parts responsible for producing stimulating signals for regulating the appetite. These include frontal, insula, anterior cingulate, and orbital cortices. Sleep disruption is known to alter the functioning of these regions of the brain, thereby having an impact on the appetite. Most primitive areas of the brain, like the amygdala and the ventral striatum, have a very strong implication that governs food intake and potentially leads to binge and weight gain.

Sleep loss causes a rise in appetitive choices for high-caloric and weight-gain-promoting foods. This is because of poor recruitment of the cortex and enhanced firing of neurons in the amygdala.⁵

As previously mentioned, levels of leptin are reduced, causing lowered satiety during sleep with a parallel rise in ghrelin that promotes more food intake because of sleep disruptions. Orexin or hypocretin has a stimulating effect on both appetite and wakefulness. It is well-known that sympathetic drive reduces during sleep, and it is the inhibitor of leptin release in the body. Recurrent restrictions in sleep decreased both the rhythm and amplitude of leptin release, which has an impact on the appetite significantly.⁵

Sleep and Limbic System

The limbic system is the emotion-regulating center of the body. The prefrontal cortex, hippocampus, and amygdala form the limbic system together.⁶

There exists a two-way relationship between sleep and emotion. Rapid eye movement sleep plays a vital role in restoring appropriate emotions every day and enhances the processing and consolidation of memories that are associated with emotions. It was found that sleep deprivation of as little as 5 hours can result in emotional dysregulation. Accumulated sleep loss was shown to result in amplified negative emotions in the brain and result in reduced functioning of the individual. Sleep disruptions are highly correlated with impulsive aggressive behaviors and behaviors that can promote suicidal behaviors.⁶

Sleep and Cognition

The mechanism of poor sleep and its association with cognitive decline is not well-understood, but it is well-known that aging causes advanced thinning of the cerebral cortex, especially in frontotemporal regions that play a role in cognition. Excessive sleep induces a proinflammatory state by increasing the interleukin-6 and C-reactive protein activity in areas of the brain, resulting in the production of a similar effect as that found in aging, which plays

an important role in cognition. It is also suggested that short sleep duration can also cause impaired cognition indirectly by setting fatigue.

Sleep deprivation results in increased plasticity of synapses in the hippocampal regions that possibly can impair cognition. Studies also revealed that even a single night of sleep deprivation can elevate the tau protein, which can accelerate the neurodegenerative process and result in Alzheimer's disease.

Sleep facilitates memory consolidation, but the mechanism is poorly understood. Many models were suggested, like memory replay, synaptic homeostasis, and neuromodulation, but these are not yet clear. Cognitive impairment from sleep deprivation, in general, is linked to two processes, one from a lapse in attention and alert fatigue and the other that the area of the brain responsible for cognition (frontal cortex) has vulnerability to sleep deprivation.

Circadian Rhythm

The circadian rhythm is maintained by the hypothalamus as well as the release of melatonin. The suprachiasmatic nucleus (SCN) of the hypothalamus receives light stimulus from the retina and sends these signals to the dorsomedial hypothalamic nuclei, which regulate the day–night cycles and melatonin release.⁷

On a genomic level, the circadian rhythm is regulated more specifically by Clock Genes, which are expressed on a 24-hour basis. Two proteins, BMA11 and Clock Proteins, bind and activate the Period and Cytochrome Genes, which create products to regulate the periodicity of the sleep–wake cycle. The binding site of these products has a negative feedback mechanism to inhibit their own synthesis for homeostatic regulation. These same products play a role in metabolism, signal transduction, and other cellular processes.⁷

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders (CRSDs) are disturbances in sleep, whether physiological or due to environmental stimuli.

- *Advanced Sleep-phase Disorder (ASPD)*

Advanced sleep-phase disorder involves waking up earlier than the routine or desired time. It can be due to an autosomal-dominant mutation in the Clock Genes, or even due to lack of exposure to entrainment agents. The symptoms may include insomnia, where sleep maintenance is necessary, and compensation of sleep deficit by sleeping in the late afternoon or evening. Diagnoses of ASPD can be done with patient history, monitoring a sleep diary, actigraphy, and other markers of the circadian rhythm such as core body temperature.⁷

- *Non-24-hour Sleep–Wake Syndrome (Hyperthermic Syndrome)*

Hyperthermic syndrome is characterized by a longer circadian rhythm with progressively delaying sleep–wake timings. This is due to asynchronous communication between the external sleep–wake cycle and the endogenous pacemaker regulating sleep, which could be due to the loss of light stimuli at the retinal ganglion cells. This is commonly seen in blind patients but may affect other individuals who have an endogenous circadian rhythm that is above the 24-hour period. Symptoms may include excessive sleepiness, early awakening, and insomnia, which result in dysfunctional daily activities. Diagnoses of hyperthermic syndrome can be conducted by monitoring the patient's sleep diary or actigraphy.⁷

Treatment for blind individuals includes resynchronizing the communication of the endogenous pacemaker with the external sleep–wake cycle via behavior modifications and healthy sleep

hygiene techniques. Pharmacologically, low doses of melatonin may also be useful if behavioral therapy fails to show improvement.⁷

- *Irregular Sleep–Wake Rhythm*

Irregular sleep–wake rhythm is characterized by having no distinguishable pattern for the sleep–wake cycle. This may be due to physiological dysfunction in the brain that inhibits the generation of the circadian rhythm. The dysfunction can be due to brain injury, dementia, and mental retardation.⁷

Treatment includes behavior modification to consolidate sleep at night and maintain alertness during the day. Pharmacologically, melatonin is also useful for patients with psychomotor retardation dealing with this disorder.⁷

- *Shift-work Sleep Disorder*

Shift-work sleep disorder is due to the partial adjustment of the endogenous circadian rhythm to the external day–night cycle. This is characterized by shift work-induced disturbance. Symptoms are expressed as having non-refreshing sleep, insomnia, and excessive daytime sleepiness, with the severity of symptoms expressed more so in the early morning and late night. Treatment of shift-work sleep disorder is influenced by the number of shifts in the patient's work schedule and the frequency of rotation for how often they work night shifts compared with day shifts.⁷

- *Jetlag Syndrome*

Jetlag syndrome is considered a temporary disorder due to changes in the environment with respect to the individual's endogenous sleep cycle. This is due to rapid travel across time zones with delayed adaptation to maintain a circadian rhythm. Symptoms range in severity depending on the range of travel across time zones and the time needed for the body to adjust.

Jetlag syndrome tends to be self-resolving and may not require treatment, however, short-term usage of melatonin and caffeine is known to alleviate the symptoms. Intermittent bright light in the morning prior to eastward travel also tends to reduce symptom severity.⁷

- *Substance Abuse and Sleep*

Substance abuse, such as unhealthy consumption of alcohol or tobacco, leads to acute disruption in sleep by affecting the homeostatic mechanisms that work alongside the sleep–wake cycle. Substance abuse can vary in its mechanism of action but tends to disrupt the duration, quality of sleep, and sleep latency via direct and indirect stimulation.⁸

For example, drug interactions that stimulate the dopamine pathway will increase arousal in patients, thus providing benefits in the treatment of narcoleptic patients. Unregulated use of drugs such as amphetamines, cocaine, and opiates can lead to sleep disruption through endocannabinoid receptors that alter the sleep–wake cycle. Withdrawal from such drugs can lead to terrible insomnia. It is hypothesized that orexin plays a role in addition to substances, and thus plays a role with sleep disruptions. Drug-induced insomnia can lead to the patient relying on further drug use to compensate for daytime fatigue, thus creating a synthetic, unhealthy circadian rhythm of its own.⁸

- *Coronary Artery Disease, Hypertension, and Sleep*

There is an association between sleep duration and the development of coronary artery disease (CAD). This can be attributable to autonomic dysregulation, which alters the sympathovagal balance during the sympathetic activity of sleep. An increase in sleep-sympathetic activity puts an individual at risk for developing

hypertension, which is more noticeable in sleep-deprived states or short durations of sleep.⁹

Sleep deprivation can affect physiology with disruption to the SCN–PVN autonomic axis. This axis sends and receives signals from the suprachiasmatic and paraventricular nuclei, known to influence insulin release from the pancreas, and glucose reuptake by the liver. Sleep deprivation interfering with this axis will lead to errors in metabolism homeostasis, which contributes to the pathophysiology of cardiac disease.⁹

Recent studies reveal that regardless of the baseline status of patients, both normotensive and hypertensive individuals show an increase in blood pressure when recorded during ambulatory blood pressure monitoring studies. Furthermore, studies also revealed that cells release more interleukin-2 *ex vivo* during sleep, which initiates plaque activity of atherosclerotic lesions. This increase in IL-2 release contributes to the risk of cardiovascular-related disease. It was also evident that the response of natural killer cells (NK cells), IL-2, and high-sensitivity C-reactive protein gets reduced when a patient is partly sleep-deprived.⁹

Sleep deprivation releases a large amount of catecholamines that can contribute to the risk of developing cardiovascular diseases. All of the factors discussed above along with sympathetic system-induced salt retention and vasoconstriction contribute to atherosclerosis as well as heart disease.⁹

Indirectly, sleep deprivation can cause a predisposition to developing insulin resistance, low leptin-raised ghrelin and low testosterone secretion, and pancreatic function downregulation, which are all symptoms found in obesity, diabetes, and increased risk of cardiovascular disease.⁹

- *African Sleeping Sickness*

Exposure to the *Trypanosoma brucei* parasite from the bite of a Tsetse fly can cause hepatosplenomegaly, arthralgia, posterior cervical lymphadenopathy, and weight loss. This parasite is predominately found in Sub-Saharan Africa. *Trypanosoma gambiense* is the sub-species that causes West African Sleeping Sickness, while the *Trypanosoma rhodesiense* causes East African Sleeping Sickness.¹⁰

African Sleeping Sickness can also be transmitted through blood transmission, sexual transmission, and even possibly organ transplant from a previously infected host to a new host.

Infection from *T. brucei* will allow the parasite to enter the central nervous system and cause neuropsychiatric conditions such as somnolence, nocturnal insomnia, hallucinations, delirium, attention deficits, confusion, and mania. It can progress to more severe symptoms such as abnormal reflexes, seizures, and even placing the patient into a coma.¹⁰

Treatment for African Sleeping Sickness involves early detection via microscopic wet-mount preparation. Serological testing can also be done but is not widely available for international use. Once detection is proven positive, pharmacological treatments include suramin, pentamidine, and melarsoprol.

- *Autosomal-dominant Frontal Lobe Epilepsy (ADNFLE)*

Autosomal-dominant Frontal Lobe Epilepsy is characterized by clusters of seizures, while the individual is asleep. It is proposed that this condition results from a genetic mutation of the *CHRNA2* and *CHRNA4* genes.¹¹ These genes tend to regulate synaptic transmissions. So, when they become desynchronized due to mutations, this leads to seizures.

The duration of these seizures can range from just a few seconds to minutes and can form mild sleep disruptions to sudden

movements such as bicycling-like activity or limb flinging. Crying and moaning also coexist with ADNFLE but may be misdiagnosed as a nightmare disorder. There is no cognitive impairment associated with these seizures.

- *Revenge Bedtime Procrastination*

Revenge bedtime procrastination occurs in individuals who sacrifice their sleep time for leisurely activities due to their nonpermitting busy schedules. It is a way to compromise sleep by making more time for entertainment.¹²

Symptoms include low daytime productivity, risk of accidents while driving, poor sleep quality, and higher fatigue. This can influence cognition with mental dulling, poor memory, stress, irritation, and even depression. If symptoms are not treated early, this may progress to the development of psychosis.¹²

Treatment of revenge bedtime procrastination includes behavior modification or pharmacological therapy.¹²

- *Bipolar Disorder's Effect on the Circadian Rhythm*

Bipolar-I and bipolar-II disorder can present sleep disruptions according to the phase the patient is in. The manic phase is characterized by the reduced need for sleep, while the depressive phase is associated with hypersomnia. This affects circadian rhythm by hormonal imbalance from the suprachiasmatic nucleus, which includes melatonin and cortisol release.

Bipolar-I disorder is more strongly correlated with the fragmentation of REM sleep, with an increased sleep latency period. On an EEG, a greater number of sleep spindles and K-complexes can be seen in patients associated with bipolar-I disorders.

- *Caffeine-induced Sleep Disorder*

Caffeine is a CNS stimulant that causes a delay in sleep onset. Caffeine acts on the adenosine receptors in the brain, causing arousal and cognition, while also indirectly increasing norepinephrine release. This ultimately enhances neuronal production like a panic attack. Long-term consequences lead to hypertension and metabolic syndrome. Caffeine-induced sleep disorder can result in the reduction of total sleep time, with altered sleep quality, leading to reduced slow-wave sleep.¹³

- *Cataplexy*

Cataplexy is described as the episodic sudden onset loss of voluntary muscle control with the sensation of muscle weakness. Episodes can be mild to severe, of which total collapse and inability for the patient to move or speak are noted. The duration of each episode also varies, from a few seconds to minutes. Cataplexy is seen with narcolepsy sleep disorder, Niemann–Pick Type-C Disease, Prader–Willi Syndrome, Angelman Syndrome, and other injuries.¹⁴

- *Narcolepsy*

Narcolepsy is described as excessive daytime sleepiness associated with hypnagogic and hypnopompic hallucinations, with common characteristics of sleep paralysis. Narcolepsy occurs due to decreased REM sleep latency and sudden shift into the REM stage or the deep-sleep stage.¹⁵ There are two types of narcolepsies known, further described in detail under the "Other Parasomnias" section.

- *Bruxism*

Bruxism is teeth clenching or grinding commonly seen in the 3rd stage of NREM. Bruxism may occur due to the result of neurotransmitter imbalance in the brain and certain SSRIs such as fluoxetine and paroxetine.¹⁶

Symptoms of bruxism can present themselves such as teeth abrasion, headaches, lockjaw, jaw pain, and the wearing down of enamel, exposing the underlying dentin. Uncontrolled bruxism can lead to temporomandibular joint pain and facial pain.¹⁶

Treatment of bruxism involves behavior therapy, using mouthguards, and biofeedback therapy. If these treatments fail to reduce symptoms, electrical stimulation of jaw muscles may be utilized as a last resort.¹⁶

- *Chronotherapy*

Chronotherapy is the exposure to bright light to reset the circadian rhythm of the body by delaying the sleep–wake timings over a long period. Modulating light intensity can help reset the circadian rhythm, although this treatment modality is not acceptable with good sleep hygiene and strict compliance treatment methods.

Chronotherapy light exposure ranges from 2000 to 10,000 Lux for 3 hours. This treatment modality requires strict compliance to be utilized in practice for melatonin safety, and thus, is less favored than behavioral therapy and educating patients regarding good sleep hygiene.

- *Obstructive Sleep Apnea*

Obstructive sleep apnea occurs due to the complete or partial collapse of the airway during sleep. This can be due to multiple factors such as pharyngeal muscle hypotonia, hypognathous jaw, congenital tongue malformations, and wide neck circumference.¹⁷

Symptoms of obstructive sleep apnea include noisy loud breathing with gasping and jerking movements of the body. The patient may relate the symptoms of daytime sleepiness, reduced concentration, lethargy, confusion, and possibly impaired driving, making them more prone to accidents. Secondary symptoms due to nighttime hypoxia can lead to cardiac arrhythmias, systemic hypertension, pulmonary vascular remodeling, and pulmonary artery hypertension.¹⁷

To diagnose obstructive sleep apnea, polysomnography can be utilized to measure the AHI (apnea–hypopnea) index. If symptoms are present, and the AHI score is greater than 5, then obstructive sleep apnea can be used as a diagnosis. Even if there are no symptoms present, the AHI score is greater than 15, obstructive sleep apnea can be used as a diagnosis.¹⁷

Treatment involves using a CPAP or BIPAP machine to support continuous balanced air pressure. For more severe, nonresolving cases, oral devices such as the mandibular advancement device are used. Other noninvasive treatment options include hypoglossal nerve stimulation, adenoidectomy, and tonsillectomy.¹⁷

- *Central Sleep Apnea*

Central sleep apnea is typically seen in patients with neuromuscular disorders such as ALS, stroke, cerebrovascular accidents, or heart failure that secondarily cause dysfunction in the respiratory center. Symptoms manifest with Cheyne Stokes's breathing pattern, with crescendo–decrescendo periodic breaths.¹⁷

The exclusion diagnosis of congenital central sleep apnea (Ondine's curse) is characterized by severe hypoventilation during sleep. The cause is unknown, but treatment includes patients requiring ventilatory support.¹⁷

Effective treatment of complex sleep apnea includes adaptive servo-ventilation. This device learns the patient's breathing patterns and adjusts them accordingly.¹⁷

- *Confusional Arousal*

Confusional arousal occurs when the patient awakens during the transition from a deep stage of sleep to a light stage of sleep.

Confusional arousal is caused by high-grade fevers, migraine attacks, and irregular sleep schedules.

The symptoms include awakening disoriented, confused, and with no recall of the episode. These episodes occur in the first part of sleep and have no associations with dreams. The drunkenness-like state right after arousal can be induced by stress, a family history of parasomnia, or insufficient sleep.

Diagnosis of this condition can be due to polysomnography and a sleep diary, while treatment of this condition is to establish good health hygiene.¹⁸

- *Exploding Head Syndrome*

Despite the name of the condition, the syndrome is completely benign and painless. This may be due to a brief elevation of sensory neurons in the brain, or dysfunction in the inner ear. It can also sometimes occur due to withdrawals of SSRIs or benzodiazepines.

The symptoms include loud noises or explosive crashing sounds that only patients can hear right before they fall asleep, or imaginary loud noises that wake them up in the middle of the night. These episodes are due to sensory shock, which is due to heightened anxiousness and difficulty falling asleep, palpitations, and dyspnea.¹⁹

There is no approved pharmacological treatment, however, tricyclic antidepressants and calcium channel blockers may be useful.

- *Klein–Levin Syndrome*

Klein–Levin syndrome is commonly seen in adolescent males and may be due to an autoimmune condition, or dysfunction in areas of the brain that regulate sleep, appetite, and body temperature.

The symptoms include lethargy, apathy, confusion, disorientation, hypersomnolence, compulsive hyperphagia, and behavioral changes such as hypersexuality and increased sexual drive. Episodes of this condition are sudden in onset with flu-like symptoms, childishness, hallucinations, and excessive sleep. These symptoms tend to subside on their own and may be due to infection, trauma, toxins, or psychological disturbances.²⁰

- *Morvan Syndrome (Morvan Fibrillary Chorea)*

A condition in which the neurons of the hypothalamus, raphe nucleus, and locus coeruleus become dysfunctional (dysautonomia), Morvan syndrome does not have an exact cause, but there is an association with the presence of autoantibodies against voltage-gated potassium channels. Morvan syndrome may also be due to possible heavy metal poisoning or exposure, and rare associations with legionella and staphylococcal infections.²¹

The symptoms include encephalopathy, peripheral nerve hyperexcitation, and dysautonomia. Differential diagnosis of this includes limbic encephalitis and neuromyotonia. Treatment of Morvan syndrome consists only of plasma exchange therapy with immunosuppressants.²¹

- *Nocturnal Enuresis*

Nocturnal enuresis is characterized as the inability to control the bladder during the sleep–wake cycle. Bladder control becomes developed in most children by the age of 5–7 years. Recurrent bedwetting during sleep may be due to the underlying medical conditions such as UTI, constipation, obstructive uropathy, ADHD, and neural tube defects such as spina bifida.

Adult nocturnal enuresis is classified as the inability to control urine retention during sleep in individuals older than 18. This may be due to other underlying conditions such as psychological/emotional problems, sickle cell, neurological disorders, or genetic predisposition.

Treatment involves enuresis alarms, feedback conditioning, and pharmacological treatment utilizing desmopressin analogs and amitriptyline.²²

- *Sleep-related Eating Disorder (Parasomnia)*

Sleep-related eating disorder is a type of parasomnia known as "Sleep-Eating". It is classified as the unconscious act of eating while asleep. Parasomnia occurs during the NREM sleep cycle, and thus, it is difficult for the individual to arouse or awaken while performing this behavior. Certain drugs, such as Zolpidem (a known treatment for insomnia) and sedatives, are known to produce such symptoms.²³

This condition can be distinguished from night-eating syndrome (NES), as NES is a type of eating disorder where individuals arise in the middle of the night to eat and have full recollection of doing so the following morning. Sleep-related eating disorders may lead to hazardous injuries such as burns or accidental poisoning by eating nonfood substances.²³

Primary sleep-related eating disorders are idiopathic in origin, whereas drug-induced sleep-related eating disorders tend to be due to sedatives. Treatment for either subtype involves behavior modification, sleep hygiene, and pharmacological agents such as serotonin reuptake inhibitors.²³

- *Orthosomnia*

Orthosomnia is described as an unhealthy obsession with obtaining perfect sleep. The patient develops a fixation to optimize sleep performance via sleep trackers or devices and tends to discredit polysomnography and actigraphy testing from medical professionals.

Symptoms that patients may express include anxiety, irritability, fatigue, and poor concentration due to unhealthy obsession. In situations such as this, it is recommended to reduce screen time to overcome the suppression of melatonin production from blue light.²⁴ Treatment would include educating the patient regarding proper sleep hygiene techniques.

- *REM Sleep Behavior Disorder (RMSBD)*

REM sleep behavior disorder is considered the failure to inhibit the sympathetic response during REM sleep. This disorder is associated commonly with synucleinopathies such as Parkinson's disease, Lewy body dementia, narcolepsy, and limbic encephalitis. Symptoms are present during the REM stage of the sleep cycle when there should be a loss of voluntary muscle tone. It is speculated that the pontomedullary junction may have altered brainstem circuitry to be causative of such a disorder.²⁵

It involves complex behaviors such as the patient having the ability to enact their dreams. Patient's unconscious actions can range from shouting in their sleep, to flailing, kicking, and other aggressions, that they will have no recollection of when they wake up in the morning. Patients may also report an altered sense of smell, dysautonomia, and gait changes in the morning, with mild impairment in cognition.²⁵

Diagnoses of this treatment can be conducted via polysomnography, focusing on atonia and behavior during sleep. Diagnostic criteria include motor or vocal symptoms that can be documented via a polysomnogram and failure to explain these symptoms due to any other medical conditions.²⁵

Symptoms can become more aggravated with the use of antidepressant medications. Treatment includes placing the patient in a safe environment to avoid injury and pharmacological intervention such as melatonin and benzodiazepines such as Clonazepam.²⁵

NREM-related Parasomnias

NREM-related parasomnias are disorders that occur during the first three stages of NREM sleep with limited responsiveness, awareness, and memory regarding the episode.

- *Sleep-walking (Somnambulism)*

Somnambulism, commonly known as "Sleep Walking", is the limited awareness to navigate an individual's environment, which may result in loss of balance, coordination, and near-collisions with the individual's surrounding environment. Somnambulism may be due to sedative-hypnotic drugs, alcohol, and other mental disorders.

- *Night Terrors (Pavor Nocturnus)*

Pavor nocturnus, commonly known as "Night Terrors", are highly prevalent in individuals that have a history of severe trauma or post-traumatic stress disorder (PTSD). The individual will have episodes of crying, screaming, whimpering, and expressions of fear during their sleep with difficulty awakening.

- *Sleep-related Abnormal Sexual Behaviors*

Sleep-related abnormal sexual behaviors, commonly known as "Sexsomnia", are characterized by initiation of sexual activity or stimulation of genitalia during the NREM sleep cycle.

REM-related Parasomnias

REM-related parasomnias include multiple types of disorders, including RMSBD. These episodes typically occur during the transitional phase from wakefulness to sleep.²⁶⁻²⁸

- *Sleep Paralysis*

Sleep paralysis is described as a brief loss of muscle tone and inability to move the body while the individual is falling asleep or as they are just waking up.

- *Nightmare Disorder*

Nightmare disorder is characterized by recurrent dreams that tend to be quite vivid and distressful. Unlike night terrors, nightmare disorders are recollected by the individual once they are awake and conscious. Individuals with severe nightmare disorders may suffer from symptoms of fatigue, confusion, and distress.

- *Catathrenia*

A sleep-related breathing disorder where the individual will have episodes of breath-holding and expiratory grunting. This is entirely different from obstructive sleep apneas and somniloquy (noisy breathing during inhalation). Catathrenia sounds are often high-pitched and squeaky. These symptoms tend to be reported by the individual's bed partner.

Other Parasomnias

- *Sleep-talking (Somniloquy)*

Somniloquy, more commonly known as "Sleep-Talking", may be incoherent in nature or expands to full conversations without the ability to recall any of the events. It can occur in all states of sleep and has no specific treatment but goes away with age for most children.²⁸

- *Sleep-related Disorders in Parkinsonism*

Parkinsonism is a neurodegenerative disorder that is predominately associated with motor conditions as well as sleep fragmentation present with early onset. This is due to the significantly increased melatonin production during tremors. Melatonin production is not as high in akinetic and rigid patients. On a neuronal level, neurons 42 and 43 have altered mechanisms of the brain by lowering the levels of orexin.²⁹

Mood disorders commonly coexist with Parkinson's and play a role in poor sleep quality. It often has an association with nocturnal limb dystonia or restless leg syndrome. The symptoms of nocturnal limb dystonia result from the "off" phenomenon, also called the striatal toe, in which toe extension becomes extremely painful. This plays a role in poor sleep quality and causes sleep disruption. The symptoms of restless leg syndrome are described as the intense urge to move one's leg that potentially interferes with sleep.²⁹

Overall, sleep disturbances are quite common in people with Parkinson's. Diagnosis of these types of disorders can be done carefully with history-taking and pharmacological treatment such as melatonin and clonazepam. Treatments with dopaminergic drugs were found to advance the nocturnal melatonin release.²⁹

• Sudden Infant Death Syndrome (SIDS)

Just as the name describes, SIDS is the death of a healthy newborn (less than 1 year of age) with an unidentifiable cause after an autopsy. It was hypothesized by Kopp, that an enlarged thymus can narrow a newborn's trachea and cause asphyxiation. Kopp named this phenomenon "Thymic Asthma". Alternatively, another hypothesis is that exposure to stress trauma and pain in utero can overwhelm the neonatal system, resulting in sudden death. This phenomenon is known to be the "Wear and Tear" Phenomenon.³⁰

Risk factors that may lead to such conditions include male gender, premature birth, cigarette smoke exposure, sleep position, and other intrinsic, extrinsic, and associated factors.³⁰

Narcolepsy

Narcolepsy is described as a chronic sleep and neurologic disorder affecting 1 in every 2000 people.¹⁵ Typical characteristic features include cataplexy, excessive daytime sleepiness (EDS), disrupted nighttime sleep, sleep paralysis, hypnopompic hallucinations and/or hypnagogic hallucinations.^{15,31-34} Narcolepsy type 1 (NT1) is associated with positive cataplexy whereas Narcolepsy type 2 (NT2) has no association with cataplexy.

Narcolepsy type 1 is caused by low levels of orexin, which is a neuropeptide that stabilizes wakefulness, and regulates arousal and appetite with cataplexy.³⁵ It is hypothesized to be autoimmune destruction affecting the hypothalamus (responsible for secreting orexin). The cause of NT1 may be due to immune-related factors, genetics predisposition, or environmental factors such as exposure to streptococcal infection or H1N1 infection and vaccination.^{36,37} Narcolepsy type 2 has normal orexin levels without cataplexy and unknown cause.

Strong positive emotions activate the reticular-activating system (RAS). Reticular-activating system in turn promotes arousal neurotransmitters as well as suppresses gamma-aminobutyric acid (GABA) to increase motor neuron activity.

With low RAS activity, orexin level decreases, ultimately causing muscular atonia. However, in NT, the inconsistent signaling of REM-suppressing neurons causes inhibition of RAS, leading to rapid wake and sleep transition cycles. Recent studies confirm other metabolic disorders and complications of dysregulated orexinergic systems, including obesity and type-2 diabetes.³⁷

Diagnosing narcolepsy includes getting a clinical history that plays a crucial role which includes evaluation of a patient's sleep log with actigraphy for 2 weeks before any further testing, to ensure that the patient is getting at least 6 hours of sleep per night.³⁸

Overnight sleep polysomnography (PSG) study is also used to exclude other possible causes of EDS. PSG may reveal rapid-onset REM sleep transition and light-fragmented sleep.

If the PSG study is positive, the next step is to do the Multiple Sleep Latency Test (MSLT). Multiple Sleep Latency Test may reveal short sleep latency and measures the extent of daytime sleepiness and how quickly REM commences.³⁸

Diagnostic criteria for narcolepsy based on ICSD-3 (International Classification of Sleep Disorders Third Edition): (1) orexin-1 deficiency or positive findings in PSG/MSLT and cataplexy; (2) to distinguish between NT1 and NT2 by the presence of cataplexy and CSF hypocretin levels; and (3) sleep latency of less than 8 minutes with one SOREMP on MSLT.³⁸

Narcolepsy is thus diagnosed (according to the DSM-5) as a history of sleep attacks for 3 months, with a frequency of 3 times per week with an irrepressible desire to have frequent naps throughout the day, and if there is an orexin-1 deficiency in the cerebrospinal fluid. The use of neuroimaging techniques, including functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) and positron emission tomography (PET), are under investigation to improve the diagnosis of narcolepsy.

TREATMENT

Nonpharmacological therapy includes behavior modification by modifying an adequate and healthier sleep schedule with 15–20 minutes naps, which is considered an effective adjunctive treatment. Other lifestyle modifications include maintaining a regular nighttime routine, avoiding sedentary activities, and psychological support such as emotional support and mental health counseling.

Pharmacological therapy differs based on precipitating symptoms such as Ehlers–Danlos syndrome (EDS) and epilepsy.

Ehlers–Danlos syndrome is treated by psychostimulants such as armodafinil to inhibit dopamine reuptake and promote wakefulness. Second-line treatment for EDS includes the use of amphetamines, which promote the release of norepinephrine and enhance dopamine efflux with potent EEG arousal, Methylphenidate has a more favorable safety profile compared with amphetamine. Solriamfetol is a newer drug, recently approved in the United States to treat EDS as it has fewer side effects compared with other drugs used for EDS.

For patients dealing with cataplexy, treatment includes venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Other classes of antidepressants recommended for cataplexy are selegiline, a monoamine oxidase type-B inhibitor and fluoxetine, a selective serotonin reuptake inhibitor (SSRI).

The only drug used to treat both cataplexy and EDS is sodium oxybate, a form of gamma-hydroxybutyrate.

CONCLUSION

It can be ascertained from the above that the role of sleep function in the human body is not just limited to metabolic repair but also to all other physiological activities which when become unbalanced can disturb the homeostatic milieu of the body. Studies are yet to demonstrate many other associations that sleep can have especially with the primitive limbic system and finer aspects of cognitive functions as well as their role in associated disorders.

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