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Sleep Physiology, Abnormal States, and Therapeutic Interventions

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ABSTRACT

Sleep is essential. Unfortunately, a significant portion of the population experiences altered sleep states that often result in a multitude of health-related issues. The regulation of sleep and sleep-wake cycles is an area of intense research, and many options for treatment are available. The following review summarizes the current understanding of normal and abnormal sleep-related conditions and the available treatment options. All clinicians managing patients must recommend appropriate therapeutic interventions for abnormal sleep states. Clinicians' solid understanding of sleep physiology, abnormal sleep states, and treatments will greatly benefit patients regardless of their disease process.

INTRODUCTION

Sleep is categorized into two kinds of sleep: rapid-eye-movement (REM) sleep and slow-wave sleep (formerly referred to as non-REM sleep). These two kinds of sleep are studied and evaluated through polysomnography (PSG), the aggregate of observed behaviors, electroencephalography (EEG), and electromyography (EMG). During REM sleep, EEG records high-frequency, low-voltage signals that originate in the pontine reticular formation.[1] Slow-wave sleep is characterized by low-frequency, high-amplitude EEG patterns. Slow-wave sleep is likely controlled by areas of the anterior hypothalamus, basal forebrain, and ventral lateral preoptic region.[2] Research on the regulation of sleep and sleep-wake cycles has shown that these cycles involve many neurotransmitters with proven roles.[1,2]

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Measuring Sleep

During PSG, multiple electrical signals are recorded, requiring the placement of 10-20 electrodes in locations on the head and body. PSG monitors electrical activity in the muscles of the eyes, chin, and lower extremities to ensure accurate sleep staging. During the process, respiration is monitored either pneumatically via nasal cannula or acoustically. Other parameters may be measured depending on the focus of evaluation.[3]

Sleep Architecture

Slow-wave sleep consists of 4 stages.

Stage 1 occurs at the onset of sleep and is characterized by normal muscle tone, eye movement, and low-voltage EEG wave patterns of mixed frequency. These low-voltage EEG wave patterns of mixed frequency are referred to as theta waves. Theta waves are the predominant wave pattern of light sleep. They first emerge in infants at 5 months of age. The amplitude of theta waves peaks at 2-4 years and declines slowly through life. Stage 1 sleep lasts only a few minutes. In Stage 1, the sleeper may be easily awakened and may deny having been asleep.

Advancement to Stage 2 begins when K-complexes and sleep spindles that last at least 0.5 second establish themselves on a background of theta

waves. The K-complex is the most prominent feature of Stage 2 and may be elicited by an auditory stimulus. Sleep spindles are high-frequency bursts (12-16 Hz) of electrical activity. Muscle tone persists during Stage 2. Eye movements during Stage 2 are generally slow or absent, although they may reappear for short intervals.

An EEG pattern of 20%-50% high-amplitude, low-frequency (2 Hz) delta waves signifies the onset of Stage 3. Sleep spindles and K-complexes can still be identified.

Progression to Stage 4 is defined as an EEG pattern of more than 50% high-amplitude, low-frequency waves. Muscle tone and eye movement are greatly diminished or absent during Stages 3 and 4.

The most recent characterization of slow-wave sleep from the American Academy of Sleep Medicine divides it into three phases: N1, N2, and N3. In Phase N1, alpha waves with frequencies of 8-13 Hz change to theta waves with frequencies of 4-7 Hz. Phase N2 is marked with the advent of sleep spindles that range from 11-16 Hz and K-complexes. Phase N3 (also called deep sleep) has an EEG pattern of 20%-50% high-amplitude ($>$ 75 microvolt), low-frequency (2 Hz) delta waves.

REM sleep has 2 components—phasic and tonic. The phasic component is marked by increased muscle activity in the eyes and face. The tonic component is the absence of muscle tone. Classic EEG features of REM sleep include high-frequency, irregular waveforms and the absence of K-complexes, sleep spindles, and low-frequency waveforms. The irregular waveforms unique to REM sleep have a sawtooth appearance and are present in bursts lasting up to 5 seconds. In terms of EEG readings, REM sleep most closely resembles the waking state. REM sleep is also characterized by diminished or absent deep tendon reflexes, irregular breathing in both frequency and tidal volume, penile tumescence, and increased variability in cardiac rhythm.

Slow-wave sleep and REM sleep alternate approximately every 90 minutes.[4] The pontine reticular formation regulates the cycling between the two. Slow-wave sleep is achieved by the release of the inhibitory substances gamma-aminobutyric acid (GABA), galanin, and adenosine. These inhibitory substances partially suppress the release of stimulating neurotransmitters such as norepinephrine, histamine, acetylcholine, serotonin, and orexins.[4]

A specific subset of cholinergic neurons within the pontine reticular formation seems to dictate the nature of REM sleep. During slow-wave sleep, these cholinergic neurons also suppress the activities of aminergic neurons. The transition from slow-wave sleep to REM sleep can be partially attributed to a reduction in the suppression of aminergic neurons.

Function of Sleep

Speculation regarding the function of sleep abounds because research has never definitively identified sleep's purpose. Despite this lack of clarity, the importance of sleep for mammals in the maintenance of homeostasis is undisputed.[5] Conservation of sleep—REM sleep in particular—throughout mammalian species suggests an evolutionary advantage, although the metabolic demand placed on neurons during REM is great.[6]

Early theories about the function of sleep focused on memory consolidation and learning, but recent evidence does not support this position.[7,8] An alternate theory states that arousal and readiness are the main reasons for REM sleep. Studies have shown that people awakened from REM sleep are more alert and functional than people awakened from slow-wave sleep in stages 3 or 4. The readiness in different states of sleep may have provided an evolutionary advantage.[9]

DYSSOMNIAS

For the purposes of this work, dyssomnia is any disorder outside of parasomnia that includes but is not limited to insomnia, hypersomnia, obstructive sleep apnea (OSA), central sleep apnea (CSA), mixed sleep apnea, restless leg syndrome (RLS), periodic limb movement disorder (PLMD), and circadian rhythm disorders (CRDs). We classify these disorders under dyssomnia because they share a marked reduction in the amount and in the quality of sleep. Dyssomnia differs from parasomnia in that dyssomnia does not include any action. We elucidate further the different major manifestations of dyssomnia below.

Insomnia

Insomnia involves both nonrestorative sleep and decreased daytime functionality and is often multifactorial with contributions from genetics, psychologic disorders, diet, physical disorders, and primary sleep disorders such as RLS and poor sleep habits. Insomnia is a ubiquitous complaint of nearly all patients at some point in life but disproportionately affects females and older patients.[4] One-third of adult respondents to an epidemiologic study performed at Stanford University[10] complained of insomnia, yet recognition and treatment of insomnia and other sleep disorders remain low among healthcare providers. Patients with psychiatric and medical disorders are at increased risk for insomnia.[11]

Organic causes of insomnia are rare. Most organic insomnia occurs because of the dysfunction of the

thalamic tracts of the ascending reticular formation that regulate sensory input into the thalamus and cortex. Organic insomnia can occur because of biological clock dysfunction; an example is the altered release of melatonin from the pineal gland.[12,13] The molecular dysfunction for sleep regulation has been observed in patients with Alzheimer disease, fatal familial insomnia, Parkinson disease, and Lewy body dementia.

The classification of insomnia is based on the length of time a patient consistently experiences both nonrestorative sleep and decreased daytime functionality. Transient insomnia lasts for 1 week or less and is usually associated with acute changes in stress levels, sleep/living environment, and severe depression. Acute insomnia lasts 1 to 4 weeks. Insomnia lasting 1 month or more is chronic and can be either primary or secondary to another disorder. The severity of insomnia may also be assessed as mild, moderate, or severe. These assessments are based on social and occupational impairment, irritability, daytime fatigue, and tiredness. Identifying the cause of insomnia requires taking a detailed history and performing a thorough physical examination.

Iatrogenic causes are not uncommon. Many classes of medications are associated with an increased incidence of insomnia. Decongestants such as pseudoephedrine and phenylephrine, respiratory medications including theophylline, and beta-2 agonists such as albuterol prolong the time needed to fall asleep. Corticosteroids including prednisone and dexamethasone have also been implicated in causing insomnia, especially when patients take them a few hours before attempting to fall asleep. Not surprisingly, attention deficit hyperactivity disorder treatments that include amphetamines, including methylphenidate, have been implicated in reducing the ability to sleep. A common yet seldom reported cause of insomnia and restlessness relates to activating antidepressants. Physicians and patients rarely associate new onset insomnia with recently prescribed medications such as selective serotonin reuptake inhibitors (SSRIs) and other antidepressants, including bupropion and duloxetine, that are common causes of insomnia in patients being treated for depression and anxiety disorders. Often a simple change of medication therapy can help patients resume normal sleep patterns.

Clinicians should always ask patients with new insomnia about recent changes in their daily caffeine intake before considering a medicinal treatment.

Physicians must evaluate daytime functionality in insomnia patients to assist both diagnosis and direct treatment. Patients who fall asleep during the day tend to suffer from chronic insomnia secondary to other conditions such as RLS, PLMD, sleep apnea, and CRD. Patients who cannot or do not have the desire to sleep during the day tend to suffer from primary insomnia such as idiopathic insomnia or psychophysiologic insomnia. These patients may also experience acute insomnia secondary to anxiety or depression.[4]

Selected insomnia subtypes are as follows:

- Adjustment insomnia is temporary (lasting less than 3 months) and directly associated with stress. After removal of or adaptation to the stressor, the insomnia usually resolves.[14]
- Psychophysiologic insomnia is chronic and characterized by heightened states of arousal or anxiety based on the lack of sleep. Patients may be affected by intrusive thoughts and the inability to relax at bedtime.[14]
- Paradoxical insomnia is chronic (lasting for 3 months or more) and characterized by a mismatch between the patient's subjective sleep estimates and objective PSG measurements that demonstrate little or no sleep. Rare nights of adequate sleep may occur.[14]
- Idiopathic insomnia is chronic with childhood onset, no identifiable cause, and no periods of remission.[14]

Inadequate Sleep Hygiene

Inadequate sleep hygiene relates to improper sleep scheduling, poor or inappropriate diet, engagement in stimulating activities near bedtime, and/or the inability to maintain a comfortable sleep environment for at least 1 month.[14] It has been held that insomnia shares an intimacy with inadequate sleep hygiene. Some have classified inadequate sleep hygiene as a form of insomnia. Others contend that inadequate sleep hygiene provides a causative factor for insomnia.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is the primary affliction that defines hypersomnolence syndromes. Patients are unable to remain awake at desired times. The effects of these disorders take a high socioeconomic toll.[3] Studies estimate the prevalence of hypersomnia in North America as 0.3%-16.3%.[15]

Narcolepsy belongs to the EDS class of sleeping disorders, a category that also includes various types of hypersomnias and insufficient sleep. Hallmark features of narcolepsy include cataplexy (a sudden episode of muscle weakness triggered by emotions), hypnagogic hallucinations, and sleep paralysis. However, these features are neither diagnostic nor required for the diagnosis of narcolepsy. Weight gain and

parasomnias such as sleepwalking and nightmares are commonly associated with narcolepsy. The prevalence of narcolepsy in the general population is 0.02%-0.18%. Genetic components have been discovered and noted. First-degree relatives have a 1%-2% chance of developing the disease. The known genetic markers are human leukocyte antigen (HLA) DRB1*1501, DQA1*0102, and DQB1*0602, among others.[16]

A strong association between narcolepsy and diminished cerebrospinal fluid levels of hypocretin-1, a promoter of wakefulness, exists. This neuropeptide hormone promoter is produced in the hypothalamus. Other evidence identifies hypocretin as a major integrator of metabolic and circadian cycles.[5] Spectroscopy studies have shown clear hypothalamic neuronal damage in patients with narcolepsy,[3] and researchers have speculated that narcolepsy may stem from the autoimmune attack of hypocretin neurons in the hypothalamus secondary to infections. Recent data that highlight the relationship among season, childhood infection, and specific HLA and T-cell polymorphisms have led some to propose a cause for the autoimmune attack. These data may support models of molecular mimicry or bystander activation of the immune system against these neurons.[17,18] Although infection is associated with the onset of narcolepsy in children and adults, autoantibodies that target hypocretin neurons have yet to be identified.

Obstructive Sleep Apnea

OSA is characterized by inspiration against a closed upper airway during sleep. Inspiration against a closed airway can lead to intermittent hypoxemia, hypercapnia, and exaggerated negative intrathoracic pressures. These results in turn may lead to significant cardiovascular morbidity. Hypertension, heart failure, pulmonary hypertension, cardiac arrhythmia, cardiac ischemia, and stroke are all associated with OSA. The prevalence of OSA may be as high as 25% in some populations.[19] Prevalence increases with elevated body mass index. The numerous risk factors for OSA can be distilled into three main categories: airway, skeletal, and soft tissue.

To maintain the patency of the upper airway and counter negative intrathoracic pressure, pharyngeal reflexes immediately precede inspiration. The impairment of these reflexes may reduce the contractile power of the muscles of the upper airway during sleep. Of particular importance are the genioglossus and geniohyoid muscles in patients with OSA; these muscles exhibit decreased contractility during sleep and increased contractility during waking hours.[3] Theories suggest that the detection of initial airflow into the oropharynx stimulates contraction of the geniohyoid and genioglossus. However, impaired muscle activation may stem from abnormal sensory nerve function secondary to acoustic vibration.

The configuration of the mandible and hyoid bones plays an integral part in the maintenance of airway patency. The size, shape, and location of the mandible determine the posterior position of the tongue. When gravity acts on the tongue, the tongue can fall to the back of the oropharynx and obstruct the flow of air. The hyoid bone also plays an integral part in the positioning of the tongue during sleep. Inferior displacement of the hyoid bone is associated with increased risk of developing OSA because the bone serves as an anchoring point and support structure for the tongue.

The soft tissues of the pharynx can encroach on the airway and cause narrowing. Allergies, infections, and trauma can cause edema and swelling of these tissues, possibly resulting in obstruction during sleep. Obesity is a well-documented risk factor for OSA.[19] A greater collapsibility of the upper airway, an increased effort for breath, and the compromised function of pharyngeal musculature are secondary to fat infiltration. Weight reduction increases the cross-sectional area of the upper airway and may ameliorate the severity of OSA.

Hormonal, developmental, and genetic factors may also contribute to the development of OSA. For example, testosterone may play a role in the development of OSA by inducing bulk in parapharyngeal musculature or manipulating the central distribution of fat. Obesity is directly linked to OSA and is highly influenced by genetics. Developmental factors include chronic nasal obstruction during childhood. Oral breathing may manipulate craniofacial development in a manner that supports OSA development. Upper airway obstruction has been shown to induce changes in mandibular development in children, and these changes may lead to jaw configurations that predispose to OSA.[20] Moreover, hormonal factors and developmental factors may stem from a genetic source, depending on the specific case.

The minimum requirement for the diagnosis of OSA is 5 10-second episodes of apnea in 1 hour. The apnea must be associated with frequent arousal, bradytachycardia, or arterial oxygen desaturation. Associated features include loud snoring, morning headaches, and excessive sleepiness with reduced sleep latency. The presence of sternal retractions and the generation of negative intrathoracic pressure distinguish OSA from CSA.[21]

Central Sleep Apnea

CSA lasts 10 or more seconds as the result of decreased respiratory drive. Unlike in OSA, large

negative intrathoracic pressures are not generated because little or no inspiratory effort is involved. Despite the increasing prevalence of sleep apnea, CSA represents a small fraction of apnea cases.[22]

CSA results from the derangement of blood pCO_2 sensory mechanisms.[23] The metabolic control of inspiration is mediated by nuclei in the dorsal respiratory group (DRG) of the medulla. The DRG also receives information from cranial nerves IX and X. Inspiration is driven or suppressed by signals from stretch receptors in the lungs, peripheral chemoreceptors, and central chemoreceptors that monitor cerebrospinal fluid. Lesions that affect the DRG, cranial nerves IX and X, chemoreceptors, and motor function may result in CSA.[23]

CSA may resemble simple periodic breathing: the patient stops breathing and then resumes at a normal ventilatory rate. CSA may also resemble Cheyne-Stokes breathing, characterized as a crescendo-decrescendo pattern of apnea/hypopnea alternating with hyperpnea.[24] Cheyne-Stokes breathing is often observed in people with congestive heart failure[25] or neurologic[26] disorders. Cheyne-Stokes breathing is further characterized as nonhypercapnic CSA (NHCSA). Current wisdom indicates that NHCSA can be caused by congestive heart failure that contributes to the delayed detection of the O_2 and CO_2 content of blood from the lungs.[23] This delay produces asynchrony between blood gas levels and respiration. The asynchrony, in turn, allows a gradual accumulation of CO_2, followed by decline of CO_2. NHCSA is also observed during chronic renal failure, periodic breathing at high altitude, and nasal continuous positive airway pressure device titration.[27-29]

The diagnosis of CSA is similar to OSA with one major exception: PSG records periods of shallow or absent breathing in patients with CSA. During apneic episodes, the patient will have no sternal retractions because of insufficient inspiratory effort. Frequent body movements, gasps, grunts, choking, and cyanosis may be observed.[21]

Mixed Sleep Apnea

Mixed sleep apnea combines OSA and CSA, with an initial cessation of respiratory drive followed by a gradual increase in respiratory efforts against obstruction.

Restless Leg Syndrome

RLS is characterized by undesirable sensations such as tingling, itching, pricking, and burning in the legs. Characteristically, movement of the affected limb(s) results in patient relief. Sleep disturbance with daytime sleepiness is a common feature of RLS. Patients with RLS have reported difficulty both with sleep onset and sleep recurrence after being awakened.[30]

The prevalence of RLS varies depending on the population. Current estimates range from 1% to 29%. RLS appears to affect women and older persons more than men and young people, with a reported frequency of 3% among people younger than 30 years of age and a frequency of as much as 19% among people older than 80 years of age.[31,32] Consensus on the pathophysiology of RLS remains unresolved. Recent studies have reported RLS symptom alleviation with dopamine receptor agonist treatments, including pramipexole and ropinirole.[33-35] This treatment implicates dopamine dysregulation of RLS. Low cerebrospinal fluid and serum ferritin levels have also been observed in patients with RLS; however, no causal link has been found to date.[3]

Diagnostic criteria for RLS as defined by the National Institutes of Health are undesirable sensations in the legs before sleep, an irresistible urge to move the limbs, the experience of partial or complete relief after movement of the affected limbs, and the return of symptoms upon abeyance of movement.[36] Although the diagnostic criteria focus on sensations that occur before sleep, patients often complain of these sensations while sitting and while watching TV at the end of the day. RLS may be considered a secondary disorder when it presents with or after the onset of another medical condition. Iron deficiency, pregnancy, renal failure requiring hemodialysis, type 2 diabetes mellitus, and a lack of physical exercise have all been associated with RLS.[37-39]

Periodic Limb Movement Disorder

PLMD is the repetitive movement of limbs that disrupts sleep. PLMD is similar to RLS, and the 2 disorders may share the same spectrum of disease. PLMD distinguishes itself from RLS in that patients with PLMD report a need or strong desire to move, but they do not experience tingling or burning of the legs.[3] The diagnosis of PLMD requires a history of EDS and severe sleep disturbance documented by PSG.

Circadian Rhythm Disorders

CRDs are an asynchrony between the sleep/wake cycle of the body and the light/dark cycle of the day. Circadian rhythms stem from the habituated physiologic and behavioral patterns in an average 24-hour period. At night, chemical promoters of sleep are released that limit sensory input through the thalamus to the cortex. During the day, the opposite is true. Six recognized CRDs currently exist: delayed sleep phase disorder, non-24-hour sleep/wake syndrome,

advanced sleep phase disorder, irregular sleep/wake rhythm, shift work sleep disorder, and jet lag disorder. The last 2 disorders result from activities that conflict with the intrinsic circadian rhythm. Both endogenous and exogenous factors contribute to CRD.

The suprachiasmatic nucleus of the hypothalamus regulates circadian rhythms in mammals. The intrinsic circadian cycle in humans is actually slightly longer than 24 hours. As a result, environmental cues such daylight factor greatly in the establishment of synchrony. Subjective improvements in mood and adjustments of circadian clocks are both possible. For example, shift workers have shown mood improvements and circadian clock adjustment because of the stimulation of environmental cues, such as bright light.[40]

Diagnosis of CRD is based on the inability to sleep when sleep is desired. Sleep architecture is otherwise normal in CRD, but patients complain of insomnia because of the delayed onset of sleep. Specific diagnostic details are discussed below.

Delayed sleep phase disorder is most common during adolescence and presents as sleep onset insomnia and difficulty in waking at a conventional time. Whether the pathogenesis involves intrinsic pathology or socially reinforced behavior is unclear. Psychophysiologic insomnia must be ruled out before the determination of a definitive diagnosis. Although the etiology is unknown, proposed theories include hypersensitivity to evening light and an inability to advance in sleep phases.[41,42]

Non-24-hour sleep/wake syndrome, also known as free-running disorder, occurs when a patient is not synchronized with the 24-hour day/night cycle. Instead, the patient has a longer circadian rhythm. The removal of cues such as clocks, access to daylight, and regular feeding schedules can induce an asynchronous rhythm of 24.15- to 24.5-hour cycles.[43] Uncommon in the general population, this syndrome is quite common among people who are completely blind because their sleep cycles cannot be entrained by the light-dark cycle.

Advanced sleep phase disorder presents as a stable sleep schedule with sleep onset several hours before the conventional or desired time. No strict guideline exists for how advanced the sleep onset must be to make the diagnosis. Instead, the diagnosis focuses on the degree of difficulty experienced in the attempt to adhere to the desired schedule. Unaffected people typically reach their lowest core body temperature between 4:00 am and 5:00 am, but patients with advanced sleep phase disorder achieve the lowest core body temperature earlier than expected. Patients with familial forms of the disorder achieved lows roughly 7 hours earlier than expected.[43]

For patients with irregular sleep/wake rhythm, the sleep acquired in a 24-hour period is broken into random, irregular bouts. PSG and actigraphy studies of patients with irregular sleep/wake rhythm demonstrate decreased slow-wave sleep at night, increased nighttime wakefulness, and increased daytime napping. The cause is unknown. However, a proposed etiology includes damage to the suprachiasmatic nucleus. Experimental ablation of the suprachiasmatic nucleus in animals results in sleep patterns similar to those observed in humans with dementia.[44] A tentative relationship exists between irregular sleep/wake rhythm and genetic factors. The possibility of this relationship has been observed in sleep studies with Alzheimer disease patients. However, further examination of this possible link is required.[45]

PARASOMNIAS

For the purposes of this work, parasomnia is any disorder outside of dyssomnia that includes arousal disorders, parasomnias associated with REM sleep, and enuresis. We classify these disorders under parasomnia because they share a marked reduction in the amount and in the quality of sleep. Parasomnia differs from dyssomnia in that the disorders of parasomnia include irregular actions executed during the sleep process. We elucidate further the different major manifestations of parasomnia below.

Arousal Disorders

Arousal disorders involve arousal from slow-wave sleep, as well as motor and sensory activation. Typical features include occurrence of the parasomnia in the first third of the night, a strong family history, retrograde amnesia about the event, arousal events restricted mostly to childhood with cessation after puberty, and nonaggressive and nonstereotypical behaviors.[3]

In terms of family history, the likelihood of developing sleepwalking increases tenfold after diagnosis of a first-degree relative.[46] Researchers have hypothesized that arousal disorders may be precipitated by benzodiazepines, alcohol, antidepressants, and stress. However, only a minority of patients who ingest these drugs develop an arousal disorder. Taking a comprehensive family history and acquiring information from sleep partners and parents may offer the most accurate means for diagnosis.

Arousal disorders include sleep terrors, sleepwalking, and confusional arousals. Confusional arousal and sleepwalking form a continuum. One extreme includes behaviors such as sitting up in bed with a fixed gaze. The other extreme includes complex behaviors such as driving a vehicle or cooking. In between these 2 extremes are behaviors such as

uttering words, conducting unintelligible conversations, engaging in sexual intercourse, and executing automatisms. Sleep partners and parents of patients often report difficulty or resistance during the attempt to wake the sleeper, and the sleeper often experiences varying degrees of amnesia upon awakening. Sleep terrors occur in sleep states 1, 3, or 4 and cause the patient to wake in a terrified state. Sleep terrors are a more sensory-focused arousal disorder with manifestations of fear such as screaming, weeping, tachycardia, mydriasis, and diaphoresis.

Parasomnias Associated With REM Sleep

Recurrent isolated paralysis, REM sleep behavior disorder, and nightmare disorder are parasomnias associated with REM sleep.

Recurrent isolated paralysis develops when wakefulness overlaps with the muscle atony of REM sleep or cataplexy. The absence of daytime sleepiness distinguishes recurrent isolated paralysis from narcolepsy and other hypersomnias. However, recurrent isolated paralysis and narcolepsy share clinical features, and patients with both are unable to move even one finger upon waking. Recurrent isolated paralysis can usually be diagnosed based on history alone if hypersomnias or psychiatric disorders are not suspected.

REM sleep behavior disorder is the condition of abnormally violent actuation of dreams during REM sleep followed by disturbed sleep. Acute REM sleep behavior disorder is associated with withdrawal from addictive substances, and chronic REM sleep behavior disorder is a neurologic, psychiatric, or endocrine abnormality. The association of this disorder with neurodegenerative diseases such as multiple system atrophy, dementia with Lewy bodies, and Parkinson disease is strong.[47-49] REM sleep behavior disorder dysfunction occurs at the level of the brainstem, where voluntary muscle tone should be completely suppressed but is not. Medications that interfere with REM physiology such as tricyclic antidepressants, SSRIs, and cholinesterase inhibitors can all induce REM sleep behavior disorder.[3] Video PSG with EMG is required for diagnosis.

Nightmare disorder is diagnosed in patients who experience terrifying dreams during REM sleep. Unlike patients with sleep terrors, patients with nightmare disorder remember the dream and present only minor autonomic manifestations such as diaphoresis and tachycardia.[50] Periodic limb movements are associated with nightmare disorder. Symptoms of nightmare disorder begin as early as age 3 and tend to decrease over subsequent decades. Diagnosis of nightmare disorder does not require PSG.

Enuresis

Enuresis is recurrent involuntary urination during sleep. The majority of primary enuresis cases occur in children who have never achieved bladder control. Secondary enuresis occurs in patients who achieve bladder control but continue involuntary urination while sleeping. Enuresis possesses associations with institutionalization, sickle cell anemia, OSA, and attention deficit hyperactivity disorder. However, the strongest predisposing factor for enuresis is one or both parents having a positive history of enuresis.[51] The diagnosis of enuresis requires the patient to be at least 5 years old.

TREATMENT OF SLEEP DISORDERS

Insomnia

First-line treatments for insomnia include improved sleep hygiene, relaxation techniques, paradoxical intention, and cognitive-behavioral therapy.[52] Improved sleep hygiene means the establishment of a disciplined sleep schedule; avoidance of daytime naps; avoidance of caffeine and heavy, spicy, or sugary foods 4-6 hours before bedtime; and engaging in strenuous exercise no later than 2 hours before bedtime. Good sleep hygiene also involves a sleeping environment with comfortable bedding and temperature and noise reduction. Good sleep hygiene also restricts the use of the bed to sleep only. Improved sleep hygiene may also involve a light snack consisting of warm milk or foods high in tryptophan. Studies have shown an increase in slow-wave sleep and in sleep with delta wave EEG patterns for subjects taking tryptophan supplementation.[53,54]

Relaxation techniques such as yoga, meditation, and autogenic training help reduce anxiety and muscle tension[55] and improve the quality of sleep.[56] Paradoxical intention is a cognitive treatment for insomnia in which the patient focuses on staying awake instead of trying to fall asleep. This activity lowers performance anxiety, sleep effort, sleep-onset latency, and overestimation of the sleep deficit.[57] In cognitive-behavioral therapy, patients learn about productive sleep habits, misconceptions concerning sleep, and the proper expectations of sleep. Cognitive-behavioral therapy is more effective than hypnotic medications in treating insomnia and seems to show sustained and lasting effects after it is discontinued.[58,59]

Pharmacologic treatment options for insomnia include benzodiazepines, nonbenzodiazepines, opioids, antidepressants, melatonin, melatonin agonists (ramelteon), sedating antihistamines, and atypical antipsychotics. Among the benzodiazepines, hypnotic benzodiazepines that bind the alpha 1 subunit of the GABA(A) receptor provide the most

relief of insomnia. These drugs can be used both to help initiate sleep and to increase the length of sleep. However, benzodiazepines have also been shown to promote light sleep and decrease deep sleep.[60] Benzodiazepine use also can cause tolerance and physical dependence. Therefore, benzodiazepines generally are not recommended for use as a long-term treatment for insomnia in most patients.

Nonbenzodiazepines have a lesser effect on the alpha 1 subunit of the GABA(A) receptor; therefore, they are used for mild to moderate forms of insomnia.[61] The risk of dependence on nonbenzodiazepines is lower than the risk of dependence on benzodiazepines.

Opioids are known to decrease REM and stage 2 sleep and are appropriate for patients with pain-associated insomnia.[62]

Tricyclic antidepressants such as amitriptyline and doxepin are strong sedatives and are used as off-label treatments for insomnia.[63] For patients suffering from both depression and insomnia, the antidepressant mirtazapine decreases sleep latency and increases sleep efficiency and sleep time.[64] However, prescribing these drugs warrants careful consideration of their anticholinergic, antihistaminergic, and antiadrenergic side effects. In addition, tricyclic antidepressants can cause withdrawal symptoms and thus rebound insomnia.

Melatonin has been shown to be just as effective as some nonbenzodiazepines both in the initiation of sleep and in the regulation of sleep/wake cycles.[65] Also, melatonin does not alter sleep patterns or affect performance-related skills.[66] Melatonin agonists have proved their efficacy in the treatment of jet lag–induced insomnia and CRDs; however, these agonists have not been as effective in treating other forms of insomnia.[67] Antihistamines such as diphenhydramine and doxylamine are efficacious over-the-counter sedatives. It has been reported that antihistamines are more effective than some prescribed hypnotics.[68] Cyproheptadine has been shown to be superior to benzodiazepines in the promotion of sleep quality.[69]

Hypersomnia

The treatment options for hypersomnia are mostly symptomatic and include proper sleep hygiene and the avoidance of alcohol and caffeine. Amphetamine, methylphenidate, and modafinil are the mainstay pharmacologic treatments. Other pharmacologic treatment options include clonidine, levodopa, bromocriptine, and antidepressants, including monoamine oxidase inhibitors.[70] The hypersomnia in Kleine-Levin syndrome is treated with amphetamine, methylphenidate, and modafinil. However, these drugs do not alleviate the syndrome's signature cognitive sluggishness and altered mental states.[71] Lithium has been shown to shorten episodes involved with Kleine-Levin syndrome.[72]

Narcolepsy

The treatment of narcolepsy involves lifestyle adjustments and medication. Lifestyle adjustments involve diet changes such as eating light or vegetarian meals and avoiding heavy meals before important activities. Recommended lifestyle adjustments include planned naps during the daytime and after meals.[73] The main pharmacologic treatments are modafinil, armodafinil, methylphenidate, amphetamine, and methamphetamine.[73] Atomoxetine, a nonstimulant norepinephrine reuptake inhibitor, has been used with success and has little abuse potential.[74]

The treatment of cataplexy, a pathologic equivalent of REM sleep atonia unique to narcolepsy, involves the suppression of REM sleep with a tricyclic antidepressant. The serotonin/norepinephrine reuptake inhibitor venlafaxine has proven efficacious in the management of cataplexy.[75] Although the mechanism of sodium oxybate's active ingredient, gamma-hydroxybutyric acid (GHB), is unknown, strong empirical evidence suggests that GHB is an effective treatment for cataplexy, daytime sleepiness, and sleep disruption from narcolepsy.[73] Sodium oxybate is currently Food and Drug Administration (FDA) approved and is the standard of care recognized by the American Academy of Sleep Medicine.[76,77]

Sleep Apnea

Conservative treatments for sleep apnea include lifestyle changes such as losing weight, sleeping in the lateral decubitus position, and avoiding alcohol and hypnotic medications. Sleeping in the lateral decubitus position particularly helps sleep apnea patients with Cheyne-Stokes respiration.[78] Alcohol and hypnotic medications can contribute to sleep apnea because these drugs may relax pharyngeal muscles.[79] The treatment for moderate to severe sleep apnea involves the use of a continuous positive airway pressure device that has been shown to be extremely effective.[79] However, long-term compliance can become an issue because patients may find the device very uncomfortable.[80] Dentists can prescribe oral appliance therapy to treat moderate to severe sleep apnea; a custom mouthpiece shifts the mandible forward.[81] Also, acetazolamide has been used to encourage respiration in sleep apnea by lowering blood pH.[82]

Patients with the following conditions may have to consider surgery: unsuccessful treatment by continuous positive airway pressure device or oral appliance

therapy, anatomic features that favor surgery, and craniofacial abnormalities that impede the use of devices.[83] Maxillomandibular advancement has been found to be the most effective surgical treatment[84] for increasing positive airway space and increasing arterial oxygen concentration.[85] Patients who had maxillomandibular advancement had significant increases and benefits related to productivity, social outcome, activity level, vigilance, and sex.[85]

Restless Leg Syndrome

Treating RLS begins with the identification of any underlying conditions that may be causing RLS, including iron deficiency anemia, venous insufficiency, and thyroid irregularities. The first line of pharmacologic treatment for primary moderate to severe RLS includes gabapentin and dopamine agonists such as ropinirole, pramipexole, carbidopa/levodopa, and pergolide. The FDA approved gabapentin in April 2011.[86] Among the dopamine agonists, pramipexole is favored for its lower incidences of nausea, vomiting, and dizziness.[87] Methadone is used for severe RLS and lacks the augmentation and rebound side effects of the dopamine agonists.[88] Carbamazepine can treat painful RLS.[89]

Periodic Limb Movement Disorder

Patients with PLMD are advised to avoid caffeine, alcohol, and antidepressants because these drugs can worsen symptoms.[90] The dopamine agonists pramipexole and ropinirole are first-line treatments that reduce or eliminate limb movements and arousals.[91] Second-line treatments such as co-careldopa have been proven superior to opioids in the treatment of PLMD.[92] Clonazepam has also been successful in improving sleep for patients with PLMD.[93]

Circadian Rhythm Disorder

CRD treatment options include behavior therapy that encourages regular sleep-wake cycles, nap avoidance, and the emphatic avoidance of stimulating activities and/or consumables near bedtime.[94] Bright-light therapies—using high-intensity light at scheduled time increments of 30-60 minutes—are effective in the delay or advancement of sleep.[95] Melatonin is useful for adjusting and maintaining sleep-wake cycles.[96,97]

Arousal Disorders

Treatments for sleep terrors are typically behavioral, such as the establishment of a proper sleep schedule. Another option involves waking the patient right before the usual occurrence of the terror to disrupt the sleep cycle. Pharmacologic treatment is usually unwarranted, but the administration of diazepam before bedtime often reduces sleep terrors.[98]

Good sleep hygiene, the avoidance of sleep deprivation, the removal of dangerous items, and the bolting and locking of doors and windows before sleep reduce the risks of harmful activity from sleepwalking.[99] Low-dose clonazepam and tricyclic antidepressants are the pharmacologic treatments of choice for sleepwalking.[100]

REM Sleep Behavior Disorder

REM sleep behavior disorder is a parasomnia in which paralysis is lost in otherwise intact REM sleep. Dangerous objects should be removed from the bedroom and the mattress should be moved to the floor to reduce the risk of injury.[101] Patients should avoid sleep deprivation, alcohol, and certain medications, especially antidepressants, because they can increase REM sleep behavior disorder.[98] Research has shown low-dose clonazepam to be the most effective treatment, with a 90% success rate. Melatonin and pramipexole are also effective alternative treatments. Levodopa is preferred in patients with coexisting Parkinson disease.[102]

Bruxism

Bruxism is the grinding of teeth during sleep. The treatment of associated factors such as sleep apnea may reduce or eliminate nonhabitual bruxism.[103] Dental guards and splints may be used to ameliorate bruxism. However, these devices do not cure the condition and have not shown increased efficacy over other therapies.[104-106] A contingent electric stimulation device can be used to trigger an inhibitory reflex to relax the jaw muscles without waking the patient.[107] Biofeedback devices are also effective, such as a biofeedback headband that makes a sound during the detection of increased EMG activity in the temporalis muscle. This headband has been shown to reduce bruxism by 60%-80% in the majority of sufferers.[108] Botulinum toxin may be used for temporary relief from bruxism in severe cases.[109]

Enuresis

Participants in a study of the use of bedwetting alarms were 13 times more likely to remain dry at night.[110] However, relapses ranged from 29% to 69% and often warranted retreatment. Desmopressin has been shown to make patients 4.5 times more likely to stay dry than a placebo.[110] Amitriptyline, imipramine, and nortriptyline are also effective because of their antimuscarinic properties. Patients who underwent therapy with these drugs were 4.2 times more likely to stay dry compared to those taking a placebo. However, the relapse rate approached 50%. Also,

the patients had to confront the increased risk of side effects.[111] Waking the patient at night to try to prevent enuresis has not been shown to be effective and does not increase the success rate when undertaken in conjunction with a bedwetting alarm.[112]

CONCLUSIONS

Although the exact function of sleep is largely unknown, its physiology and altered sleep states are much better understood because of recent large-scale research and clinical investigation. Sleep hygiene, relaxation techniques, cognitive-behavioral therapy, and pharmacologic treatments provide options for many patients. In the typical clinician's practice, psychosocial and physical symptoms may ultimately be linked with an abnormal sleep condition. The clinician's solid understanding of sleep physiology, abnormal sleep states, and treatments will greatly benefit patients regardless of their disease process, and clinicians should consider referring patients with sleep disorders to specialists who can develop appropriate diagnosis and treatment options.

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This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification Competencies for Patient Care and Medical Knowledge.