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Sleep Disorders

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ABSTRACT

Sleep disorders are frequent and can have serious consequences on patients' health and quality of life. While some sleep disorders are more challenging to treat, most can be easily managed with adequate interventions. We review the main diagnostic features of 6 major sleep disorders (insomnia, circadian rhythm disorders, sleep-disordered breathing, hypersomnia/narcolepsy, parasomnias, and restless legs syndrome/periodic limb movement disorder) to aid medical practitioners in screening and treating sleep disorders as part of clinical practice.
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INTRODUCTION

Sleep is a universal function of living species, comprising one-third of human life. Poor or insufficient sleep has been associated with a wide variety of dysfunction in most body systems, including endocrine,[1] metabolic,[2] higher cortical function,[3] and neurological disorders. Disorders of sleep can manifest as complaints of either insufficient sleep, excessive amount of perceived sleep, or abnormal movements during sleep. This review article focuses on the most commonly seen sleep disorders in neurological practice (Table).

MAJOR SLEEP DISORDERS

Insomnia

More than one-third of adults experience transient insomnia at some point in their lives. In about 40% of cases, insomnia can develop into a more chronic and persistent condition.[4] The diagnosis of insomnia is made when the patient reports dissatisfaction with sleep (sleep-onset or sleep-maintenance insomnia) as well as other daytime symptoms (eg, sleepiness, impaired attention, mood disturbances) for at least 3 nights per week and last for more than 3 months.[4] Although several insomnia subtypes have been delineated (eg, idiopathic, psychophysiological, and paradoxical), diagnosis and treatment is similar.

The precise pathophysiological mechanisms underlying insomnia have not been identified yet, but some neurobiological and psychological models have been proposed. Contributing factors include behavioral, cognitive, emotional, and genetic factors.[5] These are often conceptually classified into predisposing, precipitating, and perpetuating factors.[6]

Available treatments for insomnia include pharmacological and nonpharmacological therapies. Treatment should consider other comorbidities that lead to sleep disruption, including other primary sleep disorders (eg, sleep apnea and periodic limb movement in sleep). Initial counseling and education about good sleep practices is usually helpful, and often sufficient to reduce insomnia symptoms. Good sleep habits include: keeping regular wake times (and explaining that duration of wakefulness and circadian rhythms both affect sleep onset), limiting time in bed to sleep time, use of bed for sleep/intimacy only, avoid afternoon caffeine and limit alcohol intake, and avoiding daytime napping (otherwise these should be very brief, <30 minutes, and taken in the early afternoon at latest). In cases of persistent insomnia, cognitive behavioral therapy may prove very helpful. Studies have shown that cognitive behavioral therapy for insomnia may have equal or better effect than pharmacological treatment, and that the effect is longer lasting.[7–11] Other behavioral treatment methods include sleep restriction and relaxation-based interventions.

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Pharmacological therapy may be appropriate when treatment is anticipated to be short (eg, insomnia in the setting of stress), or in addition to behavioral treatments. The choice of agent should consider: 1) predominant type of complaints −sleep initiation or sleep maintenance; 2) frequency of insomnia symptoms (nightly vs intermittent); 3) length of treatment anticipated; 4) age and comorbidities of the patient. Sleep initiation insomnia may respond well to short-acting medications, and these can be used as needed if the condition is intermittent−in this case the choice of hypnotic should depend on comorbidities. Nightly sleep maintenance insomnia may need nightly longer-acting medications, such as eszopiclone or suvorexant. Patients with comorbid anxiety or depressive symptoms may benefit from antidepressant treatment, such as mirtazapine or trazodone. A history of sleepwalking as a child should be considered a caution when using zolpidem, as it may cause complex behaviors in sleep.[12−14] Other factors such as the patient's age and sex should also be considered before starting pharmacological treatment for insomnia. In 2013, the US Food and Drug Administration (FDA) issued a warning, recommending that a lower dose of hypnotics be used to prevent next-morning impairment due to residual effect. Women appear to be more susceptible to this risk (by FDA site, see Appendix, available online).

CLINICAL SIGNIFICANCE

- Sleep disorders are common and may adversely affect health and well-being.
- While some sleep disorders are more challenging to treat, most can be easily managed with adequate interventions.
- Sleep disorders are often briefly addressed during standard medical training. This review will provide a current practical overview of the most common sleep disorders.

Overall, medications most frequently used in the treatment of insomnia include: 1) Benzodiazepines: they have the advantages of being cheap and ubiquitous, however, they are associated with various problems: excessive sedation, high frequency of falls (due to nonselective gamma-aminobutyric acid effects), hypotension, tendency to lose efficacy after longer use, muscle relaxant effect, and significant cognitive effects. 2) Other hypnotics include: zolpidem, zolpidem CR, Intermezzo (Purdue Pharma, Stamford, CT; zolpidem ultrashort acting, 1.75-3 mg), zaleplon, and eszopiclone. The advantages of these hypnotics are that some are very short acting (Intermezzo, zaleplon), and are FDA-approved for chronic insomnia treatment (eszopiclone, zolpidem CR). However, frequent problems include common side effects such as parasomnia, and over-sedation, and some also have a potential to lose efficacy. 3) Other options for insomnia treatment include: melatonin agonists (ramelteon, tasimelteon), orexin antagonist (suvorexant), antidepressants (mirtazapine, trazodone, amitriptyline), antihistamines, and other substances (eg, herbal).

Circadian Rhythm Sleep Disorders

The timing of sleep and wakefulness is maintained on one end by homeostatic factors, and on another by the endogenous circadian system.[15] Normally, the sleep phase of the circadian rhythm occurs about 2 hours after the onset of melatonin secretion. It may occur later or earlier than society-driven scheduled sleep time, resulting in a delayed or advanced sleep−wake phase disorder.

Circadian rhythm sleep−wake disorders are common.[4] In delayed sleep−wake phase disorder, sleep occurs systematically later than needed, whereas in advanced sleep−wake phase disorder, sleep occurs systematically earlier than needed. Yet in both cases, sleep length is normal and the patient is refreshed when sleeping according to his/her desired time. Delayed sleep−wake phase disorder is thought to account for 10% of patients with chronic insomnia and is particularly common in adolescents and young adults, occurring in 7%-16%.[4] Advanced sleep−wake phase disorder is estimated to occur in 1% of middle-aged adults and even more commonly in older populations. Non-24-hour circadian rhythm disorder is thought to occur in >50% of blind individuals, and up to 80% of this population complains of sleep disturbances. Twenty percent of the workforce engages in shift work and 10%-38% of this population is estimated to suffer from shift work circadian rhythm disorder.[4]

The diagnosis and treatment of circadian rhythm sleep−wake disorders are sometimes difficult without an accurate assessment of the patient's circadian phase. In research conditions, plasma measurements of melatonin, and core body temperature, are commonly used.[16] However, these are labor-intensive, expensive, require special settings, and are, therefore, impracticable for routine clinic use. More feasible assessment parameters include salivary and urine melatonin measures.[17−20] Despite their high prevalence, circadian rhythm sleep−wake disorders are commonly misdiagnosed as insomnia or, in some situations, hypersomnia. A recent study of patients diagnosed with primary insomnia demonstrated that 10%-22% had a bedtime out of phase with their circadian sleep time, suggesting a circadian etiology for their sleep problems.[21] This misdiagnosis may lead to unsuccessful, expensive, and sometimes harmful consequences.

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).[16] For non-24-hour sleep−wake phase disorder, in blind individuals, Tasimelteon has been recently found helpful. It is also helpful to counsel patients that the accuracy of the timing of any interventions for delayed sleep−wake phase disorder may be crucial to successful treatment. The effect of light, for example, depends on the light spectrum/wavelength, intensity, prior light exposure, and, most importantly,

Table Common Sleep Disorders in Neurology

Condition	Defining Features	Confirmatory Evaluations	Treatment
Insomnia	Difficulty with: • Sleep initiation or • Sleep maintenance Results in: • Fatigue/malaise • Mood disturbance/irritability • Reduced productivity Chronic: > 3 times/week and > 3 months	• Primary: clinical history • Ancillary: sleep log	• Hypnotics • Antidepressants • Melatonin agonists • Orexin antagonists
DSWPD	• Sleep occurs systematically later tha needed • Sleep length is normal and the patient is refreshed when sleeping according to his/her desired time	• Sleep log • Actigraphy* • Melatonin*	• Melatonin 0.3-3 mg — evening (5 h before habitual bedtime) • Combined with morning blue light
ASWPD	• Sleep occurs systematically earlier that needed • Sleep length is normal and the patient is refreshed when sleeping according to his/her desired time	• Sleep log • Actigraphy* • Melatonin*	• Evening blue light
OSA	• Snoring/apneas/gasping upon awakening • Other nonspecific symptoms - Morning headache - Attention deficits - Mood disturbance - Nocturia, night sweats - Aggravation of other disease	• Home sleep testing • Polysomnography In both cases, diagnosis requires: • Apnea-Hypopnea Index > 5/h with symptoms or Index > 15/h regardless of symptoms	• Continuous or bilevel positive airway pressure • Dental — oral appliances • Surgery — for select cases Conservative measures — to use with another treatment or for few symptoms and Apnea-Hypopnea Index < 20 • Sleep position • Weight loss • Avoidance of "relaxants" close to bedtime
Narcolepsy	Classic tetrad: • Sleepiness • Sleep paralysis • Hypnagogic hallucinations Type 1: Cataplexy Type 2: Without cataplexy	Multiple sleep latency test • Sleep latency < 8 min • 2 Sleep-onset REM or • 1 SOREM and first REM on polysomnography < 15 min Type 1: • Cerebrospinal fluid: low orexin† • HLA DQB1*0602	Sleepiness: • Modafinil • Armodafinil • Methylphenidate • Amphetamine salts • Sodium oxybate Cataplexy: • Sodium oxybate • SSRI
REM behavior disorder	• Abnormal behaviors, emerging from REM sleep • Occur in the later parts of the night • Typical behaviors: talking, screaming, punching, kicking • Associated with a vivid dream recall	• Clinical history • Polysomnography: REM without atonia	• Clonazepam • Other benzodiazepines • Melatonin • Treatment of associated disorders • Safety measures
NREM parasomnia	• Large variety of behaviors (hallucinations, eating, locomotion, aggression, sex, terrors) • Frequent amnesia for the event • Behaviors may be from the same group (usually eating or talking), but variable in presentation (eg, saying different phrases)	• Clinical history	• Counseling - Precipitating factors (eg, sleep deprivation, stress, fever, medications/substances) • Benzodiazepines • Antidepressants

Table (*Continued*)

Condition	Defining Features	Confirmatory Evaluations	Treatment
	• Several different behaviors can co-occur • Distinction from seizures/postictal confusion is crucial		
RLS/PLMS	RLS: • Indescribable uncomfortable sensations that make the patient move limbs • Difficulty with sleep initiation due to the above sensations and urge to move • Often associated with PLMS • Fragmented sleep, discomfort • Daytime sleepiness	• Clinical history • Polysomnography may confirm PLMS PLMS • PLMS > 15/h with symptoms	• Dopamine-agonists - Pramipexole starting at 0.125-0.25 mg or - Ropinirole 0.25-0.5 mg - The dose of dopamine agonists should be kept low • Gabapentin enacarbil • Fe supplementation if indicated (ferritin < 50), to be continued until > 100 • Opiates and benzodiazepines (more limited use)

ASWPD = advanced sleep–wake phase disorder; DSWPD = delayed sleep–wake phase disorder; NREM = non-rapid-eye movement; OSA = obstructive sleep apnea; PLMS = periodic limb movement of sleep; REM = rapid-eye movement; RLS = Restless legs syndrome; SSRI = selective serotonin reuptake inhibitor.
*Not covered by most insurances in the US.
†Not commercially available in the US.

timing.[22] The same light intensity may delay the sleep phase of the circadian cycle if administered prior to the core body temperature minimum, or advance it if administered after it.[16] For the same reasons, administration of exogenous melatonin should also be timed by circadian phase.

Sleep-Disordered Breathing: Obstructive Sleep Apnea and Central Sleep Apnea

Sleep apnea is a primary sleep disorder characterized by pauses of breathing during sleep. There are 3 main types of sleep apnea: obstructive sleep apnea, central sleep apnea, and complex sleep apnea. An obstructive apnea is defined as a cessation of airflow for at least 10 seconds, and results from the collapse of the upper away during sleep. By contrast, during a central apnea, the interruption of airflow occurs when there is a lack of effort to breathe—usually arising from the brain respiratory centers to the muscles that control breathing. Some patients present with a combination of both obstructive and central apnea, which is termed complex sleep apnea.

Sleep apnea can be diagnosed during polysomnography, where the severity of sleep apnea is quantified by the number of respiratory events per hour of sleep. Along with clinical symptoms, at least 5 events per hour (Apnea-Hypopnea Index ≥ 5) are required for a diagnosis of sleep apnea.[23] According to prevalent criteria, an Apnea-Hypopnea Index between 5 and 14 will be considered mild sleep apnea, between 15 and 29 moderate sleep apnea, and more than 30 events per hour is considered severe sleep apnea. Several screening scales for sleep apnea have been developed to identify at-risk patients. One of the most frequently used in clinic is the STOP-BANG questionnaire,[24] which contains 4 yes-or-no questions that relate to clinical signs of sleep apnea (S: snoring; T: tiredness during daytime; O: observed apnea; P: high blood pressure), as well as 4 items related to the well-known sleep apnea risk factors (B: body mass index > 35; A: Age > 50 years; N: Neck circumference > 40 cm; G: male gender). A patient is at high risk of sleep apnea if 3 or more questions are positively answered.[24]

In the general middle-aged population, moderate to severe sleep apnea can be found in about 30%-50% of men and 11%-23% of women.[25,26] Clinical symptoms include most often loud snoring, choking/gasping, apneas witnessed by the bed partner, excessive sleepiness and fatigue, and morning headache. Sleep apnea has debilitating effects on the patient and their family's quality of life. When left untreated, sleep apnea can also have major negative health consequences; it increases the risk of hypertension, type 2 diabetes, and cardiovascular diseases.[27] In a large cohort study, risk of stroke in men with moderate to severe obstructive sleep apnea increased incrementally with each unit of increased severity.[28] Sleep apnea is also a well-known risk factor for cognitive deficits.[29] The negative consequences of sleep apnea can be, at least partially, reversed by consistent and accurate treatment.

Several treatment options are available. For mild cases of obstructive sleep apnea, conservative therapies such as weight loss and avoiding supine position (for positional sleep apnea) can be helpful. The most widely used and currently first-line treatment for obstructive sleep apnea is positive airway pressure therapy. Continuous positive airway pressure consists of a continuous flow of air into the nose, while bilevel therapy provides a higher pressure on inspiration and lower level on expiration. The latter is sometimes more comfortable with higher pressures. Auto-titrating machines have been very helpful to expedite treatment. Adaptive servo-ventilation can also be used to treat complex sleep apnea. Continuous positive airway pressure therapy in obstructive sleep apnea individuals has been found

to reduce subjective daytime sleepiness, improve cognitive functioning, as well as mood and quality of life.[30–33] It also can improve blood pressure and glucose control.[34] Oral appliances such as mandibular advancement devices may also help to improve mild to moderate cases of obstructive sleep apnea that are not associated with any significant risk factors, or for patients who are intolerant to positive airway pressure therapy. Surgical treatment methods include, most commonly, soft palate surgery, nasal surgery, and maxillomandibular surgery. These may help sleep apnea severity, although they generally do not cure sleep apnea.

Hypersomnia: Narcolepsy and Idiopathic Hypersomnia

When evaluating hypersomnia, the following issues should be considered: *Is there enough sleep opportunity?* In adults, typical sleep need is more than 7 hours, with adequate, consistent timing. *Are there factors that impair sleep quality and, as a result, lead to insufficient/poor quality sleep?* These include medications and environmental factors, as well as primary sleep disorders such as sleep apnea and sleep-related movement disorders. *Does it recur more than 3 times per week, for more than 3 months?*

Disorders causing central hypersomnia are rare. They include narcolepsy type 1 (with cataplexy), narcolepsy type 2 (no cataplexy), idiopathic hypersomnia (with long sleep time or without long sleep time), and recurrent hypersomnia (such as Kleine-Levin syndrome). Narcolepsy is a disorder of rapid eye movement sleep regulation.[4] Classic symptoms include sleepiness, sleep paralysis, and hypnagogic hallucinations. Cataplexy in narcolepsy type 1 consists of a loss of muscle tone, provoked typically by positive emotions, classically, laughing or telling a joke. Occasionally, surprise or anger can be a trigger. Classically, in narcolepsy, any daytime naps are short (15-40 minutes) and refreshing. There is a common genetic association (DQB1*0602 haplotype), and patients with narcolepsy type 1 may also have lower orexin measured in cerebrospinal fluid.[35,36]

The diagnosis is made first clinically; however, an objective documentation using multiple sleep latency test is needed to confirm the sleepiness. This test is typically performed on the day after a polysomnography and consists of 5 nap opportunities. Most narcolepsy patients fall asleep within minutes of being given the opportunity, and thus a short sleep latency (average of <8 minutes over the 5 naps), as well as rapid eye movement sleep during these naps would be supportive of narcolepsy (see Figure). Current criteria require that rapid eye movement sleep is either seen in 2 or more naps or that rapid eye movement is seen in one nap along with a rapid eye movement latency <15 minutes on the preceding polysomnogram. Haplotype typing may be performed; however, it is difficult to interpret and depends on genetics. Cerebrospinal fluid measurements of hypocretin are performed in many European countries but are not currently commercially available in the US.

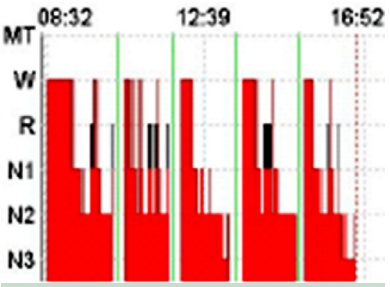

Figure Example of a multiple sleep latency test in a patient with narcolepsy. "W" delineates waking stage, N1-3 the non-rapid eye movement stages 1-3, respectively, and the black solid bars indicate rapid eye movement sleep. The green bars delineate each nap opportunity. Sleep is seen in all 5 nap opportunities, occurs within a few minutes of the lights out, and rapid eye movement sleep occurs in 3 of the 5 naps.

Treatment of the sleepiness typically starts with modafinil or armodafinil. If these are not tolerated or ineffective, stimulants (methylphenidate or amphetamine/dextroamphetamine) can be used. Cautions should include monitoring blood pressure and evaluating for arrhythmias, which can be worsened by these medications. None of these have been approved for use in pregnancy. Cataplexy responds to antidepressants (typically selective serotonin reuptake inhibitors [SSRI]) or sodium oxybate. Common comorbidities of narcolepsy include rapid eye movement behavior disorder, present in as much as 10% of narcolepsy patients,[37] as well as periodic limb movement of sleep. Both may be worsened by SSRI, including the ones used for the cataplexy treatment.

Hypersomnia can sometimes be seen after head trauma, in some reports affecting as much as half of the patients with traumatic brain injury,[38] and a quarter of these patients may have sleep-disordered breathing. Treatment of sleep-disordered breathing may be helpful, and use of any sedating medications should be judicious.

In rare conditions, hypersomnia can be idiopathic. This condition typically presents with long, nonrefreshing naps. Two types exist: 1) with a long sleep time, and 2) without long sleep time. The criteria for diagnosis include the clinical presentation, as well as supportive evidence from the multiple sleep latency test: a sleep latency <8 minutes, no sleep-onset rapid eye movement. Treatment is often challenging, modafinil or armodafinil at higher doses can be used, and sometimes other stimulants can be helpful. In another rare condition, Kleine-Levin syndrome, hypersomnia is recurrent. Kleine-Levin syndrome typically presents in adolescence or the early 20s, and consists of periods that last for approximately 2 weeks, during which patients

exhibit very long sleep (often 12-21 hours per day), and during the waking periods individuals exhibit cognitive abnormalities (eg, major apathy, confusion, slowness, amnesia), dream-like behavior, hyperphagia, or hypersexuality. Between episodes, individuals have a normal level of functioning. Treatment with lithium may decrease the frequency of episodes, while stimulants have a marginal effect during the events.[39,40]

Parasomnias: Non-Rapid Eye Movement Parasomnias and Rapid Eye Movement Behavior Disorder

Parasomnias can be grouped by type of behavior seen, or based on sleep stage from which they occur. The most common non-rapid eye movement parasomnias include somnambulism, confusional arousals, and night terrors. These parasomnias are characterized by a wide variety of behaviors, but they mostly occur from slow-wave sleep, and as such, they typically arise in the first half of the night. They most commonly manifest with directed behaviors. They are not stereotypic and may have a variable duration. Upon awakening, the patient does not have any vivid dream recall. If any dream mentation is recalled, it is very brief or fragmented. The pathophysiology of non-rapid eye movement parasomnias is not well understood, although the hypothesis of dysregulated slow-wave sleep has been proposed.[41] Treatment may involve benzodiazepines, or in some cases, tricyclic antidepressants. Clinicians should be aware that some medications may induce somnambulism; according to a recent review, the strongest evidence for medication-induced sleepwalking was found for zolpidem and sodium oxybate.[42]

Rapid eye movement parasomnias, particularly rapid eye movement sleep behavior disorder, have been studied more extensively. Typically, the patient with rapid eye movement behavior disorder will present with abnormal behaviors during rapid eye movement sleep. Dream enactment behaviors result from the loss of the normal muscle atonia seen during this sleep stage. They occur mostly in the latter part of the night and consist of a wide variety of motor activity that appears to be related to a dream. If the patient awakens during that time, he/she would be frequently able to recall the dream, which is consistent with the behavior exhibited, and is often elaborate. The type of behavior that most commonly brings the patient to medical attention is often violent, such as screaming, punching, kicking, or other such movements, however, nonviolent activity can be seen as well.

Along with a history of recurrent dream-enactment behaviors, the diagnosis is confirmed by nocturnal polysomnography, which shows typical muscle activations during rapid eye movement sleep or in some cases may record the abnormal events. This sleep disorder is frequently linked with neurodegenerative conditions, particularly synucleinopathies.[43] Differential diagnosis includes other parasomnias, conversion disorders, and seizures. Unlike seizures, rapid eye movement behavior disorder events are directed, and are not stereotypic. Identifying association with a dream is also very helpful.

The most commonly used agent for treating rapid eye movement behavior disorder is clonazepam,[44] which has to be used with caution in patients with dementia and may lead to excessive sedation. Due to the strong association with neurodegenerative conditions, patients are likely to have contraindications for benzodiazepine treatment. Another option is melatonin—an inexpensive and safer option.[45–47] In one recent study, melatonin was found to be equally effective as clonazepam for reducing the frequency of dream-enactment episodes.[48]

Restless Legs Syndrome and Periodic Limb Movements of Sleep

Restless legs syndrome is characterized by an uncomfortable sensation, leading to an urge to move the limbs that occurs or worsens while at rest, with consistent evening predominance, associated with dysesthesia, and is partially relieved by physical activity. Patients often describe the sensation as "creeping, crawling tingling" or shock-like feelings, or simply indescribable discomfort. Over the course of the disease, the sensations can spread to the arms or trunk. One of the major characteristics of restless legs syndrome is its worsening in the evening and at night, which results in difficulty initiating sleep, as patients often get up and pace around the room to relieve the discomfort. In turn, poor sleep often leads to fatigue and daytime sleepiness.

Restless legs syndrome is one of the most common sleep-related movement disorders, affecting about 15% of adults.[49] Generally, it affects women more than men, and prevalence is also higher with advancing age.[49] The cause can be idiopathic or secondary. In its idiopathic form, there is no known cause, but most patients will have a family history. Secondary restless legs syndrome most often has a later-onset course, and is associated with various neurological disorders (eg, multiple sclerosis, Parkinson disease), iron deficiency (low ferritin level), or pregnancy.

The diagnosis is made by clinical history. Restless legs syndrome and periodic limb movement of sleep frequently co-occur; the latter is present in 80% to 90% of patients diagnosed with restless legs syndrome. The presence of periodic limb movement in sleep is also supportive for the diagnosis of restless legs syndrome. Periodic limb movement of sleep can be diagnosed by clinical history, but a polysomnography may be useful to confirm the diagnosis, particularly in patients with unexplained symptoms of insomnia or hypersomnia.

Multiple studies highlight an important role of brain iron levels in the pathology of restless legs syndrome and periodic limb movement of sleep, but these are usually lower in patients with restless legs syndrome.[50] Dysfunction of the dopaminergic system has also been demonstrated as a potential pathophysiological mechanism for restless legs

syndrome. Evaluation of serum ferritin level is recommended. If ferritin is below 50 ug/L, replacement of iron should be considered. Otherwise, pharmacological treatment of restless legs syndrome may start with either dopamine agonists or gabapentin or gabapentin enacarbil. Levodopa, ropinirole, pramipexole, cabergoline, and pergolide are all considered efficacious. The doses of dopamine agonists should be kept as low as possible to decrease the possibility of worsening symptoms over time (termed augmentation). Other efficacious medications include pregabalin, and rotigotine. In more advanced disease, when other medications are no longer effective, or in the setting of severe augmentation, opiates can be considered. Intravenous ferric carboxymaltose and pneumatic compression devices were reported likely efficacious in idiopathic restless legs syndrome. Clonidine and bupropion seem to have insufficient evidence for efficacy at this time.[51]

A challenging long-term complication of restless legs syndrome is the development of augmentation. This phenomenon consists of earlier occurrence and worsening of the symptoms. For example, a patient who presented with typical symptom onset around bedtime (10-11 pm) reports that symptoms now occur in the early evening or afternoon, likely suffers from augmentation. To decrease the likelihood for augmentation, initial treatment may consider gabapentin or gabapentin enacarbil instead of any dopamine agonists.[52]

CONCLUSION

Sleep is vital for all living species, and as it comprises roughly one-third of our lives, when disrupted or perturbed, it can have significant negative consequences on quality of life and daytime function, and therefore, sleep disorders should be promptly treated. Where appropriate, a subspecialty referral should be considered.

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APPENDIX

US Food and Drug Administration (FDA) recommendations regarding hypnotics:

- Immediate-release products: "FDA is requiring the manufacturers of certain immediate-release zolpidem products (Ambien, Edluar, and Zolpimist) to lower the recommended dose. FDA has informed manufacturers that: 1) The recommended initial dose for women should be lowered from 10 mg to 5 mg, immediately before bedtime; 2) The drug labeling should recommend that health care professionals consider prescribing a lower dose of 5 mg for men. In many men, the 5-mg dose provides sufficient efficacy. 3) The drug labeling should include a statement that, for both men and women, the 5-mg dose could be increased to 10 mg if needed, but the higher dose is more likely to impair next−morning driving and other activities that require full alertness."
- Extended-release products: "FDA is also requiring the manufacturer of extended-release zolpidem (Ambien CR) to lower the recommended dose. FDA has informed the manufacturer that: 1) The recommended initial dose for women should be lowered from 12.5 mg to 6.25 mg, immediately before bedtime; 2) The drug labeling should recommend that health care professionals consider prescribing a lower dose of 6.25 mg in men. In many men, the 6.25-mg dose provides sufficient efficacy.