Review of Sleep Disorders

Lori A. Panossian, MD, Alon Y. Avidan, MD, MPH,*

KEYWORDS
- Insomnia
- Parasomnia
- Sleep apnea
- Circadian rhythm
- Classification
- Management

EPIDEMIOLOGY AND CLASSIFICATION

How Prevalent are Sleep Disorders and What are their Potential Consequences?

Sleep disorders are extremely common in the general population and can lead to significant morbidity. Sleep disturbances lasting at least several nights per month have been reported by 30% of the population. Sleep disorders may cause or exacerbate preexisting medical and psychiatric conditions and are associated with high rates of depression, anxiety, and impaired daytime functioning. They may also lead to poor occupational performance, motor vehicle accidents, cardiovascular and endocrine disorders, or heightened pain perception.

How are Sleep Disorders Categorized?

The International Classification of Sleep Disorders, second edition (ICSD-2) was published by the American Academy of Sleep Medicine with the goal of standardizing definitions and creating a systematic approach to diagnosis (Box 1). The ICSD-2 subdivides sleep disorders into eight major categories: insomnia, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm disorders, parasomnias, and sleep-related movement disorders.

CLINICAL APPROACH TO THE PATIENT WHO HAS SLEEP DISTURBANCES

When Should a Patient be Referred for a Sleep Study?

Although many sleep disorders can be diagnosed clinically, some require further evaluation in a sleep laboratory. In suspected sleep-related breathing disorders, a full-night polysomnogram (PSG) is recommended followed by continuous positive airway pressure (CPAP) titration. PSG is also indicated in severe forms of parasomnias, such as rapid eye movement (REM) sleep behavior disorder (RBD). Patients

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*a UCLA Department of Neurology, UCLA Medical Center, 710 Westwood Plaza 1241 RNRC, Los Angeles, CA 90095-1767, USA

*b UCLA Department of Neurology, UCLA Neurology Clinic, UCLA Sleep Disorders Center, 710 Westwood Boulevard, Room 1-169 RNRC, Los Angeles, CA 90095-6975, USA

* Corresponding author.

E-mail address: avidan@mednet.ucla.edu (A.Y. Avidan).

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who have possible narcolepsy should be evaluated with a daytime nap study, the multiple sleep latency test (MSLT), for objective quantification of hypersomnia, and PSG performed the night before to document total sleep time and evaluate for other comorbid sleep disturbances. Alternatively, insomnia and restless legs syndrome (RLS) do not routinely require PSG because diagnosis is mainly clinically derived.6 In some circumstances, a PSG may be helpful for some who present with insomnia that is refractory to traditional therapy and in whom other sleep disorders (ie, sleep apnea, motor disorders of sleep) are also suspected.

**What are Some Important Components of a Sleep History?**

The sleep history should include bedtime habits, timing of sleep onset and waking, daytime sleepiness, snoring, abnormal nocturnal leg kicking, nocturia, mood complaints, and cataplexy. Details about comorbid medical or psychiatric diagnoses, substance abuse, stressors, and family history should also be elicited.7 Information-gathering tools include daily sleep logs that patients keep for several weeks; these provide a thorough overview of their home routines and may identify environmental or behavioral contributors.7 The Epworth Sleepiness Scale (ESS) is a self-administered and validated questionnaire that quantifies the severity of daytime sleepiness; a score greater than 10 signifies significant sleepiness (Table 1).7,8

**What are the Components of a Sleep Disorders–Specific Physical Examination?**

An evaluation for obstructive sleep apnea (OSA) should include measurements of neck circumference and posterior airway size. Neck circumferences greater than 43 cm in men or 41 cm in women are associated with increased OSA risk. The Mallampati classification assigns a score to grade the severity of airway crowding, and a higher score together with nasal obstruction are risk factors for OSA (Fig. 1).7 RLS may be associated with peripheral neuropathy, and in these patients a careful sensory examination of the lower extremities is indicated. Similarly, RBD may be a harbinger for alpha synucleinopathies, such as Parkinson disease, which may be become apparent on clinical evaluation and associated with nocturnal agitation and dream enactment.7,9,10

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### Box 1

**Major categories of sleep disorders**

<table>
<thead>
<tr>
<th>International Classification of Sleep Disorders, second edition, categories of sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnias</td>
</tr>
<tr>
<td>Sleep-related breathing disorders</td>
</tr>
<tr>
<td>Hypersomnias of central origin (not due to a circadian rhythm sleep disorder, sleep-related breathing disorder, or other causes of disturbed nocturnal sleep)</td>
</tr>
<tr>
<td>Circadian rhythm sleep disorders</td>
</tr>
<tr>
<td>Parasomnias</td>
</tr>
<tr>
<td>Sleep-related movement disorders</td>
</tr>
<tr>
<td>Isolated symptoms, apparently normal variants, and unresolved issues</td>
</tr>
<tr>
<td>Other sleep disorders</td>
</tr>
</tbody>
</table>

What Objective Tests can be Used to Measure Sleep?

The PSG is the mainstay of sleep laboratory testing. It consists of electrographic recordings of multiple physiologic parameters during drowsiness and sleep. Measurements may include electroencephalography (EEG) for sleep staging, electro-oculogram (EOG) channels to measure eye movements, electromyography (EMG) measured superficially on the skin to assess for movement or atonia during REM sleep, airflow monitors, EKG leads, pulse oximetry, chest and abdominal excursion monitors to assess respiratory effort, auditory recordings of snoring, and video recording of movements in sleep.7 An example of a PSG is provided in Fig. 2 recorded during the night in a patient presenting with abnormal nocturnal behaviors and dream enactment. The clinical history was suggestive of RBD and was confirmed by the diagnostic PSG using expanded electromyographic leads documenting abnormal augmentation of the EMG tone during REM sleep and confirming RBD.

Patients who have suspected narcolepsy can undergo further evaluation with the MSLT on the morning after the PSG.7,11,12 The MSLT uses electrographic recordings to assess a series of four to five naps taken the morning after the nocturnal PSG. Patients who have excessive sleepiness fall asleep faster and have abnormal sleep latencies of less than 8 minutes. Patients who have narcolepsy are more likely to have abnormal rapid onset of REM sleep intrusion during the daytime. The PSG criteria for narcolepsy include two or more sleep-onset REM periods during the MSLT and a mean sleep latency of less than 8 minutes.11,12

Table 1

<table>
<thead>
<tr>
<th>Epworth Sleepiness Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>How likely are you to fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.</td>
</tr>
<tr>
<td>0 = no chance of dozing</td>
</tr>
<tr>
<td>1 = slight chance of dozing</td>
</tr>
<tr>
<td>2 = moderate chance of dozing</td>
</tr>
<tr>
<td>3 = high chance of dozing</td>
</tr>
<tr>
<td><strong>Situation</strong></td>
</tr>
<tr>
<td>Sitting and reading</td>
</tr>
<tr>
<td>Watching TV</td>
</tr>
<tr>
<td>Sitting inactive in a public place (e.g., a theater or meeting)</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
</tr>
<tr>
<td><strong>Total Score</strong> =</td>
</tr>
</tbody>
</table>

The ESS is an eight-point questionnaire that assesses the severity of daytime sleepiness in various situations. Adapted from Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14(6):540–5; with permission.

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INSOMNIA
Diagnosis and Epidemiology

When does insomnia meet criteria for a sleep disorder?
Patients may complain of difficulty falling asleep (sleep-onset insomnia) or difficulty remaining asleep (sleep-maintenance insomnia) with frequent nocturnal awakenings or early morning awakenings associated with nonrestorative sleep. According to a recent National Institutes of Health consensus, insomnia is defined as a disorder when occurring despite the patient’s having adequate opportunity and circumstances to sleep, and must be associated with impairment of daytime functioning or mood symptoms. Daytime impairment may manifest as inattention, impaired memory and concentration, poor performance in vocational or social settings, increased errors at work or while driving, tension headaches, gastrointestinal symptoms, or fatigue. Mood symptoms include decreased energy and motivation, irritability, restlessness, and anxiety.

How common is insomnia?
Approximately 9% to 15% of the general United States population has reported symptoms of chronic insomnia with associated daytime consequences. Similarly, the European population has an insomnia prevalence of 16.8%, with 64.5% of those also suffering from comorbid sleep or psychiatric disorders. The risk for insomnia increases in women. More than one third of the population older than 65 years of age has insomnia.
age has symptoms of insomnia. This finding seems to be related to physical inactivity, dissatisfaction with social life, and comorbid medical problems in older adults. When controlling for these factors, age alone is not a significant contributor.18

How serious a problem is insomnia?
Chronic insomnia can have a deleterious effect on patients’ comorbid medical and psychiatric illnesses. For example, insomnia can heighten the perception of pain19,20 and is associated with the development of endocrine disturbances.4,21 Insomnia may also have an association with increased risk for hypertension or cardiovascular disease.22 Insufficient sleep can lead to public health hazards, such as increased risk for motor vehicle accidents, occupational errors, and poor multitasking.3,23

Classification

What are some of the main causes of primary insomnia?
Insomnia can be primary or comorbid along with another medical or psychiatric condition. Primary insomnia can be divided into three categories: idiopathic insomnia, psychophysiological insomnia, and paradoxical insomnia (also known as sleep state misperception).15,24 Patients who have idiopathic insomnia suffer from pervasive sleep disturbance throughout their lives, beginning in early childhood, and are at risk for developing major depression and overuse of pharmacologic sleep aids or
alcohol because of distress or daytime impairment from the sleep deficit. The estimated prevalence is 0.7% to 1.0% among adolescents and young adults.5

Psychophysiologic insomnia develops as a result of maladaptive thought patterns and hyperarousal, including somatic tension, inability to relax at bedtime, racing thoughts, hypervigilance, or anxiety.5 There is also believed to be an underlying physical state of heightened arousal, with increased catecholamine levels, elevated basal metabolic rate and body temperature, heart rate changes, and increased central nervous system metabolism.25,26 Symptoms typically last one month or longer.5

Paradoxical insomnia is characterized by the complaint of severe insomnia and daytime sleepiness, but without any objective evidence of sleep disturbance. These patients typically have normal sleep patterns on PSG. Paradoxical insomnia is a rare condition with poorly understood pathophysiology.5

What comorbid disorders are associated with insomnia?
Insomnia can be comorbid with a psychiatric illness, such as depression, anxiety, or somatoform disorder; it can also occur in conjunction with medication use or substance abuse, including stimulants, corticosteroids, caffeine, alcohol, and many prescription drugs. Many medical conditions are associated with insomnia, including chronic pain, RLS, pulmonary disorders (such as chronic obstructive pulmonary disease and asthma), menopause, nocturia, and neurologic disorders.5,13

What is adjustment insomnia (acute insomnia)?
Adjustment insomnia is a short-lived sleep disturbance precipitated by anxiety from an identifiable stressor. The sleep disturbance is expected to resolve once the stressor has dissipated or the patient has adjusted. If symptoms last for more than a few months, acute insomnia may become chronic, particularly if maladaptive sleep behaviors develop, such as suboptimal stress management or poor sleep hygiene.5,27

What is sleep hygiene and how is it related to insomnia?
Sleep hygiene consists of optimizing routines and behaviors associated with sleep. Some patients develop habits that prevent the onset of relaxation and sleepiness at the appropriate time, resulting in insomnia due to inadequate sleep hygiene. Some problematic behaviors include maintaining erratic sleep and wake times, lying in bed awake for prolonged periods of time, addressing stressful or worrisome issues near bedtime, exposure to bright lights, such as TV or computer screens, around bedtime, late night eating or caffeine, nicotine or alcohol use, or prolonged daytime naps.28

Treatment

What are some nonpharmacologic treatment options for insomnia?
Cognitive-behavioral therapy (CBT) has demonstrated efficacy in treating chronic insomnia.29–31 It is recommended as the first-line therapy for primary insomnia30,32 and is also beneficial for many types of comorbid insomnia, including patient who have chronic pain, cancer, and depression. Although pharmacologic therapy may work more quickly, CBT provides better long-term sleep benefits as compared with pharmacologic therapy alone; CBT alone is also more effective than CBT combined with medication.33 A potential limitation of CBT is that resources or trained providers may not be available to administer the recommended biweekly CBT sessions.13,34

What are the current pharmacologic treatment recommendations for insomnia in adults?
Hypnotic medications are shown in Table 2 classified according to their mechanism of action and indication. Options include benzodiazepines, such as triazolam, estazolam,
and temazepam, and nonbenzodiazepine hypnotics, including zolpidem, zolpidem tartrate, zaleplon, and eszopiclone.\textsuperscript{14,35} Zolpidem and zaleplon have a short duration of action and are useful in sleep-onset insomnia, whereas longer-acting agents, such as eszopiclone, zolpidem extended-release, or temazepam, are effective for sleep-maintenance insomnia.\textsuperscript{13} The nonbenzodiazepine hypnotics have less potential for abuse, tolerance, or withdrawal,\textsuperscript{35} but may be associated with increased propensity for rebound insomnia and amnestic reactions in higher doses.\textsuperscript{14}

Melatonin receptor agonists, such as ramelteon, are a newer class of Food and Drug Administration (FDA)–approved agents for sleep-onset insomnia.\textsuperscript{35,36} Rozerem is currently the only FDA-approved medication for the treatment of insomnia that is not schedule IV and has no abuse potential. Over-the-counter melatonin is also available but is not FDA regulated, and randomized controlled trials have shown no clear benefit unless insomnia is related to a circadian rhythm disorder.\textsuperscript{37,38} Other over-the-counter sleep aids include antihistamines, such as diphenhydramine, which may reduce sleep latency but can cause side effects, such as daytime sedation and cognitive impairment.\textsuperscript{14} Antihistamines are not approved for use as sleep aids and their long-term efficacy has not been proven.

Although not FDA approved for the indication, low-dose antidepressants are commonly prescribed for insomnia. In the short term, trazodone has been shown to improve sleep in primary insomnia and in patients who have comorbid depression, but its safety and efficacy have not been studied for long-term use.\textsuperscript{14,35} Tricyclic antidepressants, such as amitriptyline and doxepin, can improve sleep efficiency but have the potential for adverse anticholinergic effects, daytime sedation, and suppression of REM sleep, resulting in REM sleep rebound with disturbing dreams; thus they are not indicated for short-term use in insomnia.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Duration of Action</th>
<th>Recommended Dose in Adults</th>
<th>Class</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>Short</td>
<td>0.125–0.25 mg</td>
<td>Benzodiazepine</td>
<td>Sleep-onset insomnia</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Intermediate</td>
<td>7.5–30 mg</td>
<td>Benzodiazepine</td>
<td>Sleep-maintenance insomnia</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Intermediate</td>
<td>0.5–2 mg</td>
<td>Benzodiazepine</td>
<td>Sleep-maintenance insomnia</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Ultrashort</td>
<td>5–20 mg</td>
<td>Nonbenzodiazepine hypnotic</td>
<td>Sleep-onset and sleep-maintenance insomnia</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Short</td>
<td>5–10 mg</td>
<td>Nonbenzodiazepine hypnotic</td>
<td>Sleep-onset insomnia</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Intermediate</td>
<td>1–3 mg</td>
<td>Nonbenzodiazepine hypnotic</td>
<td>Sleep-maintenance insomnia</td>
</tr>
<tr>
<td>Zolpidem extended-release</td>
<td>Long</td>
<td>6.25–12.5 mg</td>
<td>Nonbenzodiazepine hypnotic</td>
<td>Sleep-onset and sleep-maintenance insomnia</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Short</td>
<td>8 mg</td>
<td>Melatonin receptor agonist</td>
<td>Sleep-onset insomnia</td>
</tr>
</tbody>
</table>

OBSTRUCTIVE SLEEP APNEA
Diagnosis and Epidemiology

How is obstructive sleep apnea diagnosed?
OSA is a form of sleep-disordered breathing, consisting of episodic upper airway obstruction with reduced blood oxygenation and brief arousals from sleep. An episode of complete airway obstruction despite ongoing respiratory effort is called an apnea, and partial obstruction with persistent effort is termed hypopnea. The events typically last 10 to 30 seconds, but can last for 1 minute or longer (Fig. 3). Blood oxygenation returns to baseline immediately after the event. The severity of OSA is based in part on the apnea-hypopnea index (AHI), the ratio of apneas or hypopneas per hour of sleep measured during PSG. OSA is generally diagnosed when the sleep study demonstrates an AHI of 5 or greater and there are associated symptoms of excessive daytime sleepiness (ie, as measured by the ESS), nonrefreshing sleep, or witnessed pauses in breathing during sleep. The physical examination should include measurements of the body mass index, neck circumference, and Mallampati classification of tongue size to oropharyngeal size, all of which can confer a higher risk for OSA if elevated.

How prevalent is obstructive sleep apnea in the population?
OSA is common and can affect children and adults. Prevalence is estimated at 2% of women and 4% of men aged 30 to 60 years. Risk factors include increased age, obesity, gender, and ethnicity.

Fig. 3. A 60-second epoch (recorded during stage Rapid Eye Movement (REM) sleep) from a diagnostic polysomnogram of an older man with a history of pauses in his breathing, snoring and excessive daytime somnolence previously admitted to the stroke unit with left hemiparesis and right middle cerebral artery infarction. Obstructive sleep apnea characterized by nasal oral (N/O) breathing cessation (1) in the presence of persistent respiratory effort (2) and hypoxemia (3). An EEG arousal (4) signifies a change to a higher EEG frequency. Channels are as follows: Electrooculogram (left: LOC-A2, right: ROC-A1), chin EMG, EEG (left central, right central, left occipital, right occipital), electrocardiogram, limb EMG, snoring, nasal-oral airflow, respiratory effort (thoracic, abdominal), nasal pressure, and oxygen desaturation. The CPAP channel is inactive.
male gender, obesity, and high cholesterol. Snoring is also associated with an increased OSA risk, possibly related to snoring-induced pharyngeal edema and inflammation. Sleep-disordered breathing is increased among older adults (mean age of 76 years old), with an estimated prevalence of 24% to 26%. Among older adults, OSA with daytime sleepiness can cause significant cognitive difficulties, particularly in tests of attention. Treatment with CPAP is effective in treating the cognitive and cardiovascular sequelae of OSA in the older population.

Management

What are some behavioral interventions for obstructive sleep apnea?
Strategies aimed at minimizing airway obstruction may be beneficial in treating milder OSA, including sleeping with the head and trunk slightly elevated, avoiding the supine position at night, refraining from use of alcohol or sedatives, and weight loss. Patients who have craniofacial structural problems may be candidates for oral appliances, such as mandibular advancement devices.

What is the success rate of continuous positive air pressure?
Nightly use of nasal CPAP or bi-level positive airway pressure (BiPAP) is the mainstay of treatment of OSA. When used regularly, it is effective in reducing apneas and hypopneas and improving oxygenation and sleep, with associated improvements in daytime sleepiness and cognitive performance. The cardiovascular complications of OSA may also diminish. There is evidence that OSA is associated with systemic inflammation, with endothelial dysfunction and activated leukocytes, and that inflammation is reduced with use of CPAP. Unfortunately, there are many barriers to the regular use of CPAP for at least 4 hours nightly, with a nonadherence rate of as high as 29% to 83%. The reasons for this are multifactorial and may include physical side effects, such as nasal stuffiness, and psychologic obstacles. The physical side effects can be ameliorated somewhat by use of heated humidification, nasal sprays, and correctly fitting the mask.

What interventions are available for patients who have failed continuous positive air pressure?
In patients who have severe disease or cannot tolerate CPAP, surgical treatment of OSA may be an option. Strategies may include uvulopalatopharyngoplasty to reduce oropharyngeal soft tissue bulk, or tracheostomy in severe refractory cases associated with significant cardiovascular morbidity. Although pharmacologic treatments have not been successful as OSA monotherapy, modafinil, a nonsympathomimetic wake-promoting agent, may be used during the day in conjunction with nightly CPAP to reduce symptoms of excessive daytime sleepiness (provided that patients are compliant with CPAP, are not sleep deprived, and have documented evidence of sleepiness based on such measures as the ESS). Patients who are adequately compliant with CPAP use and continue to have excessive daytime somnolence may have other underlying sleep disorder (ie, narcolepsy) or need adjustments to their CPAP settings and should be evaluated with a repeat PSG.

NARCOLEPSY

Diagnosis and Epidemiology

How is narcolepsy diagnosed?
Diagnostic criteria include symptoms of severe excessive daytime sleepiness occurring almost daily for at least 3 months that interfere with functioning, REM intrusion phenomena (ie, cataplexy, hypnagogic hallucinations, sleep paralysis), and
electrographic evidence of an abnormal MSLT, with a sleep latency of 8 minutes or less and at least two sleep-onset REM periods following a PSG. Narcolepsy may occur with or without cataplexy. Cataplexy is defined as sudden self-limited episodes of loss of waking muscle tone, usually triggered by laughter or other strong emotions. The presence of cataplexy may be sufficient by itself to establish the diagnosis of narcolepsy and cataplexy, although sleep studies are often advised to quantitatively assess the level of sleepiness. Patients may also have episodes of sleep paralysis, hypnagogic hallucinations, and fragmented sleep with frequent nocturnal arousals. Sleep paralysis occurs as patients transition from sleep to waking, and consists of episodes up to several minutes in duration of inability to move and occasionally feeling unable to breathe despite being awake. Hypnagogic hallucinations are vivid and often frightening perceptual hallucinatory experiences, which occur during the transition between waking and sleep. Sleep paralysis and hypnagogic hallucinations may rarely occur in normal individuals also. Fragmented nocturnal sleep and automatic behaviors may also occur when patients go about their daily activities in a mechanical fashion with no memory or conscious awareness of their actions.

What is the population prevalence of narcolepsy?
Narcolepsy with cataplexy is rare, affecting approximately 0.02% to 0.18% of the general population in the United States and Europe. The prevalence ranges from as low as 0.002% in Israel to 0.15% in Japan. The disease may present at any age but is typically diagnosed before age 25. Men are slightly more likely to be affected than women.

Pathophysiology

What causes narcolepsy?
Narcolepsy arises because of interplay between genetic and environmental factors. It is hypothesized that an autoimmune process results in loss of hypothalamic neurons responsible for producing the neuropeptide hypocretin. Hypocretin normally modulates an increase in muscle tone during wakefulness. Ninety percent of patients who have narcolepsy with cataplexy and 10% of those without cataplexy demonstrate reduced levels of cerebrospinal fluid hypocretin-1. Most of these patients are also positive for the major histocompatibility class II allele HLA DQ1B*0602. Specific autoantibody markers for narcolepsy have not yet been found, however.

Narcolepsy Management

What are the treatment options for narcolepsy?
Pharmacologic therapies for excessive daytime sleepiness include stimulants and other wakefulness-promoting agents (Table 3). Although traditionally stimulants, such as methylphenidate and dextroamphetamine, were used, first-line therapy now consists of the nonstimulant medication modafinil. Modafinil has a low potential for abuse, is well tolerated, and was effective in promoting wakefulness in clinical trials. Sodium oxybate, the sodium salt of g-hydroxybutyrate, is also useful in the treatment of narcolepsy. It is a short-acting sedative hypnotic that is administered at night to help consolidate REM sleep and increase slow-wave sleep. It significantly reduces daytime sleepiness and also improves cataplexy and associated daytime symptoms of narcolepsy. Other treatment options include selegiline, a monoamine oxidase B inhibitor that can improve alertness and also treats cataplexy symptoms; however, its use in high doses is limited by the need to maintain a low-tyramine diet. Although sodium oxybate is the only approved medication for cataplexy in the United States, tricyclic antidepressants (TCAs), such as clomipramine, have
been used to treat cataplexy successfully for decades. TCAAs may cause more severe rebound cataplexy if abruptly discontinued, however. More recently serotonin and norepinephrine reuptake inhibitors have also been used for cataplexy, including fluoxetine and venlafaxine. Nonpharmacologic therapy using regular bedtimes and strategically timed power naps may also improve alertness.

### CIRCADIAN RHYTHM SLEEP DISORDERS

#### Diagnosis and Epidemiology

What are some common types of circadian rhythm disorders?

Circadian rhythm refers to the body’s internal timing system, which synchronizes its rhythmic cycles to external stimuli to follow a 24-hour day. Circadian rhythms affect sleep and wake cycles, cortisol release, body temperature, melatonin levels, and other physiologic variables. Patients who have circadian rhythm disorders have chronic or recurring sleep disturbances (insomnia or hypersomnia) because of misalignment between their endogenous circadian timing and external influences.

The most common disorder is delayed sleep phase–type, characterized by sleep and wake times that are later than desired, often resulting in daytime sleepiness when conventional waking times are enforced. Individuals typically prefer to sleep from 2 to 6 AM until 10 AM to 1 PM. Although the general population prevalence is estimated at 0.17%, it occurs in approximately 7% of adolescents and is more common in men. Advanced sleep phase–type is less common, and is characterized by earlier than desired sleep and awakening. In situations in which a conventional later bedtime is required, patients continue to awaken early and develop chronic sleep deprivation. Jet lag is another form of circadian rhythm disturbance, attributable to rapid change in time zones altering the timing of exogenous light stimuli. This alteration results in transient symptoms of difficulty falling asleep at the appropriate time and daytime sleepiness. Jet lag is often more severe among older adults whose circadian rhythms take longer to adjust.

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**Table 3**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Usual Dose in Adults</th>
<th>Class</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine</td>
<td>5–50 mg/d</td>
<td>Stimulant</td>
<td>EDS</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>10–40 mg/d</td>
<td>Stimulant</td>
<td>EDS</td>
</tr>
<tr>
<td>Modafinil</td>
<td>100–400 mg/d</td>
<td>Non-sympathomimetic</td>
<td>EDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wake-promoting agent</td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
<td>5–10 mg/d</td>
<td>Monoamine oxidase  B inhibitor</td>
<td>EDS</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>4.5–9.0 g/d</td>
<td>Gamma-hydroxybutyrate</td>
<td>Cataplexy and EDS</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>10–200 mg/d</td>
<td>Heterocyclic antidepressant</td>
<td>Cataplexy</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10–80 mg/d</td>
<td>Serotonin reuptake inhibitor</td>
<td>Cataplexy</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75–375 mg/d</td>
<td>Norepinephrine reuptake inhibitor</td>
<td>Cataplexy</td>
</tr>
</tbody>
</table>

Abbreviation: EDS, excessive daytime sleepiness.

**How can a diagnosis be made?**
Diagnosis of circadian rhythm disorders is based primarily on history and a sleep diary. Actigraphy, based on a wrist-mounted motion detector worn as an outpatient for at least 7 days, can help quantify time spent asleep. PSG is indicated only if another underlying sleep disorder is suspected.66,68

**How are circadian rhythm disorders treated?**
Delayed or advanced sleep phase–type disorders can be difficult to treat, and trials of various treatment modalities may be necessary. Management strategies include bright light therapy, chronotherapy, or melatonin. Light therapy, defined as exposure to bright light around 2500 lux for 2 to 3 hours in the mornings, has some benefit in retraining circadian rhythm to conform to conventional sleep times, especially when combined with avoiding light in the evening.66,68 Chronotherapy in delayed sleep phase disorders consists of the patient delaying sleep time by 3 hours every 2 days until he or she adjusts to a conventional earlier bedtime and wake time. Although effective in some patients, compliance and maintenance after treatment completion are difficult, and it has not been demonstrated to consistently work in advanced sleep phase disorders.66,68 Melatonin given in the afternoon or evening can also benefit patients who have delayed sleep phase.66,68

**How is jet lag disorder best managed?**
Options to minimize jet lag include behavioral strategies, such as good sleep hygiene, shifting sleep and wake times gradually before travel to conform to the destination’s time zone, and avoiding bright light exposure before bedtime.66,68 Melatonin administered before bedtime in the new time zone has also been shown to be effective, particularly immediate-release doses of 0.5 to 5 mg.68 Nonbenzodiazepine hypnotics, such as zolpidem 10 mg at bedtime, may be used for short-term treatment of insomnia due to jet lag; however, hypnotics may have a higher risk for adverse effects. Caffeine improves daytime sleepiness from jet lag but may interfere with sleep architecture.68

**PARASOMNIAS**

**Diagnosis and Epidemiology**

**What are parasomnias?**
Parasomnias consist of undesirable experiences or behaviors that occur during transitions between sleep and waking. They represent central nervous system activation and intrusion of wakefulness into REM or non-REM sleep, producing nonvolitional motor, emotional, or autonomic activity. Non-REM sleep parasomnias include confusional arousals and sleep terrors, whereas REM sleep–associated parasomnias include nightmares and RBD.69–76

**What are sleep terrors, and how do they differ from nightmares?**
Sleep terrors occur in approximately 3% of children aged 4 to 12 years and may also commonly present around age 20 to 30 years. They are dramatic sudden arousals from non-REM sleep with associated screaming, fear, and increased autonomic activity. Patients may be disoriented, unresponsive to the environment, and typically do not remember the event afterward. By contrast, nightmares typically occur during REM sleep toward the end of the night and are not associated with autonomic activity or amnesia.69,71,72,75,77 Treatment of night terrors is usually not indicated and the condition resolves over time, but severe cases may be treated with low-dose benzodiazepines at bedtime.69
How is rapid eye movement sleep behavior disorder diagnosed?
RBD consists of abnormal loss of muscle tone inhibition during REM sleep, permitting vigorous movements while dreaming. Sleep behaviors can include screaming, punching, and kicking for up to several minutes, sometimes resulting in injury to the patient or bed partner.78 RBD may be associated with unusually vivid and often violent dreams. RBD is more common in men older than 50 years of age, and approximately 40% of cases are associated with an underlying neurodegenerative condition, such as Parkinson disease or multiple system atrophy.76 There is also a high incidence of RBD among narcoleptics.69 RBD may be mistaken for nocturnal seizures, but unlike epilepsy, RBD movements are not stereotyped.70 Diagnosis is made based on clinical history and PSG, which demonstrates anomalous increases in muscle tone on EMG during REM sleep.70

Management

What are some management strategies for rapid eye movement sleep behavior disorder?
The goal of treatment is to minimize potentially injurious behaviors. Nonpharmacologic approaches include avoiding substances that may exacerbate RBD, such as antidepressants (selective serotonin reuptake inhibitors, monoamine oxidase inhibitors), caffeine, or alcohol, which can trigger RBD episodes,79–81 and removing dangerous objects from the sleep environment to improve safety. Medications include clonazepam 0.25 to 1 mg at bedtime, tricyclic antidepressants, dopamine agonists or levodopa (particularly in patients who have underlying Parkinson disease), anticonvulsants such as carbamazepine, and melatonin at high doses.69,70,78,82–85

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENT DISORDER

Diagnosis and Epidemiology

How is restless legs syndrome diagnosed?
RLS is described clinically as an overwhelming urge to move the legs or sometimes the arms, particularly worse in the evening.86,87 Succinctly, RLS can be defined as a “movement-responsive quiescent nocturnal focal akathisia usually with dysesthesias.”88 Symptoms are usually worse later in the day and may disrupt sleep initiation. RLS is diagnosed clinically based on the following four criteria: an urge to move the legs usually accompanied by an uncomfortable sensation; rest or inactivity exacerbating the urge to move the legs; physical activity temporarily relieving the urge to move the legs; and evening or nighttime predominance of the symptoms.5,89

What are some predisposing factors for restless legs syndrome?
Although the population prevalence of RLS in North America ranges from 5% to 10%, only 2.5% of patients have symptoms severe enough to necessitate clinical attention.5,90 There is a higher prevalence of RLS among older adults and women. RLS may be primary or idiopathic, and 50% of these patients also have a positive family history.5 RLS may also be secondary to other medical conditions, including pregnancy, end-stage renal disease, iron or folate deficiency, peripheral neuropathy, radiculopathy, rheumatoid arthritis, or fibromyalgia.86,90 Medications, such as antihistamines, dopamine receptor antagonists, and antidepressants (with the exception of bupropion) may exacerbate RLS.5

What are periodic limb movements in sleep?
Periodic limb movements in sleep occur in 80% to 90% of patients who have RLS and may also commonly occur in older adults who do not have RLS.5,86 Symptoms include...
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Risks</th>
</tr>
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<tbody>
<tr>
<td><strong>Iron</strong></td>
<td></td>
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<tr>
<td>Ferrous sulfate</td>
<td>325 mg bid to tid Recommended for serum ferritin &lt;50 μg</td>
<td>Gastrointestinal side effects: constipation. Role in treatment under current investigation</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
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<tr>
<td>Pramipexole</td>
<td>0.125–0.5 mg, 2–3 h before bedtime. Start low and increase slowly(^a)</td>
<td>Severe sleepiness, nausea, vomiting, sleep attacks, rare compulsive gambling, hallucinations, orthostatic hypotension</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>0.25–2 mg 1–2 h before bedtime(^a)</td>
<td>Severe sleepiness, nausea, vomiting, sleep attacks, rare compulsive gambling, hallucinations, orthostatic hypotension</td>
</tr>
<tr>
<td><strong>Dopaminergic agents</strong></td>
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<tr>
<td>Levodopa/carbidopa</td>
<td>25/200 mg: 1/2 tab to 3 tabs 30 min before bedtime.</td>
<td>Nausea, sleepiness, augmentation of daytime symptoms, insomnia, sleepiness, gastrointestinal disturbances</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
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<tr>
<td>Gabapentin</td>
<td>300–2700 mg/d divided tid</td>
<td>Daytime sleepiness, nausea</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.125–0.5 mg half hour before bedtime</td>
<td>Nausea, sedation, dizziness</td>
</tr>
<tr>
<td><strong>Clonidine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catapres</td>
<td>0.1 mg bid May be helpful in patients who have hypertension</td>
<td>Dry mouth, drowsiness, constipation, sedation, weakness, depression (1%), orthostatic hypotension</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene and acetaminophen</td>
<td>300 mg/d</td>
<td>Nausea, vomiting, restlessness, constipation. Addiction, tolerance may be possible</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>65–135 mg at bedtime</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>30 mg</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Only FDA-approved drugs for RLS as of August, 2008. 
repetitive, stereotyped limb movements occurring in sleep, typically involving the lower extremities. Diagnosis is based on PSG, which demonstrates the stereotyped repetitive movements on limb EMG during non-REM sleep.\textsuperscript{5,91}

**Management**

**What are the current treatment options for restless legs syndrome?**

Dopaminergic medications are first-line treatment of RLS, and the dopamine agonists ropinirole and pramipexole are FDA approved for this indication (Table 4).\textsuperscript{69,91–99} Levodopa may also be used but may cause augmentation, a phenomenon in which RLS symptom severity worsens and occurs earlier in the day in some patients.\textsuperscript{91,100} Second-line medications include gabapentin, benzodiazepines, clonidine, or opiates, such as oxycodone.\textsuperscript{69} Patients who have iron deficiency anemia–associated RLS should also be treated with iron supplements as adjunctive therapy.\textsuperscript{86}

**SUMMARY**

Sleep disorders are prevalent in the general population and can significantly affect physical and mental health and emotional well-being. There is a broad range of sleep disorders with varied clinical presentations. Physicians of all specialties should screen for the presence of disturbed sleep and consider referral to a sleep specialist when indicated.

**REFERENCES**


