Review of Sleep Disorders

Lori A. Panossian, MD[a], Alon Y. Avidan, MD, MPH[b,*]

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.[1] Sleep disorders may cause or exacerbate preexisting medical and psychiatric conditions and are associated with high rates of depression, anxiety, and impaired daytime functioning.[2] They may also lead to poor occupational performance, motor vehicle accidents, cardiovascular and endocrine disorders, or heightened pain perception.[1,3,4]

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**).[5] 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.[5]

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

[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).

Med Clin N Am 93 (2009) 407–425
doi:10.1016/j.mcna.2008.09.001 **medical.theclinics.com**
0025-7125/08/$ – see front matter. Published by Elsevier Inc.

Box 1
Major categories of sleep disorders

International Classification of Sleep Disorders, second edition, categories of sleep disorders

Insomnias

Sleep-related breathing disorders

Hypersomnias of central origin (not due to a circadian rhythm sleep disorder, sleep-related breathing disorder, or other causes of disturbed nocturnal sleep)

Circadian rhythm sleep disorders

Parasomnias

Sleep-related movement disorders

Isolated symptoms, apparently normal variants, and unresolved issues

Other sleep disorders

Data from American Academy of Sleep Medicine. The international classification of sleep disorders, 2nd edition: Diagnostic and coding manual. Sateia M, editor. Westchester (IL): American Academy of Sleep Medicine; 2005. p. xiii.

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]

Table 1
Epworth Sleepiness Scale

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.

0 = no chance of dozing

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

Situation	Chance of Dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (eg, a theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
Total Score =	

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.

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, electrooculogram (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]

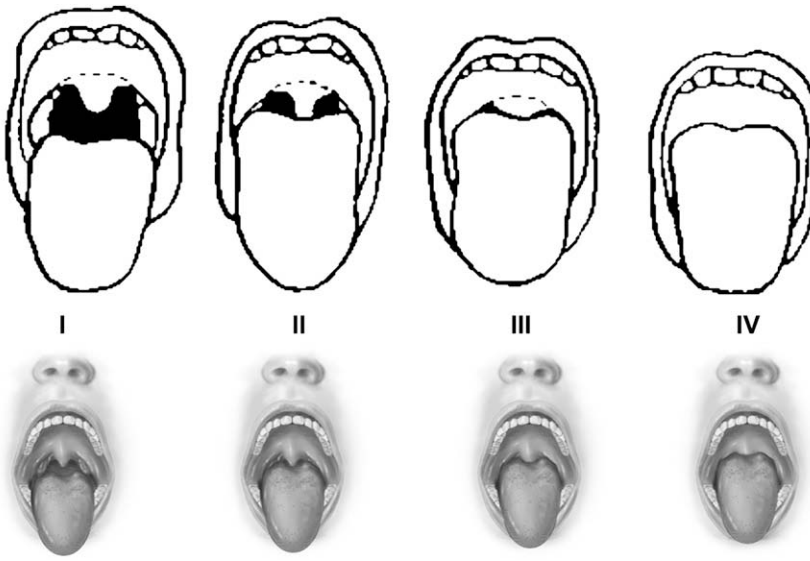

Fig. 1. Mallampati classification. The classification is determined by assessing the anatomy of the oral cavity and describes tongue size relative to oropharyngeal size. The test is conducted with the patient seated, the head held in a neutral position and the mouth wide open and relaxed. The subsequent classification is assigned based on the pharyngeal structures that are visible. Scoring is as follows: Class I: Full visibility of tonsils, uvula, and soft palate. Class II: Visibility of hard and soft palate, upper portion of tonsils, and uvula. Class III: Soft and hard palate and base of the uvula are visible. Class IV: Only hard palate visible. (*Data from* Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J 1985;32:429–34.)

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.[7,9,10,13–15] 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.[5,14,15] 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.[14]

How common is insomnia?

Approximately 9% to 15% of the general United States population has reported symptoms of chronic insomnia with associated daytime consequences.[16] Similarly, the European population has an insomnia prevalence of 16.8%, with 64.5% of those also suffering from comorbid sleep or psychiatric disorders.[17] The risk for insomnia increases in women.[16] More than one third of the population older than 65 years of

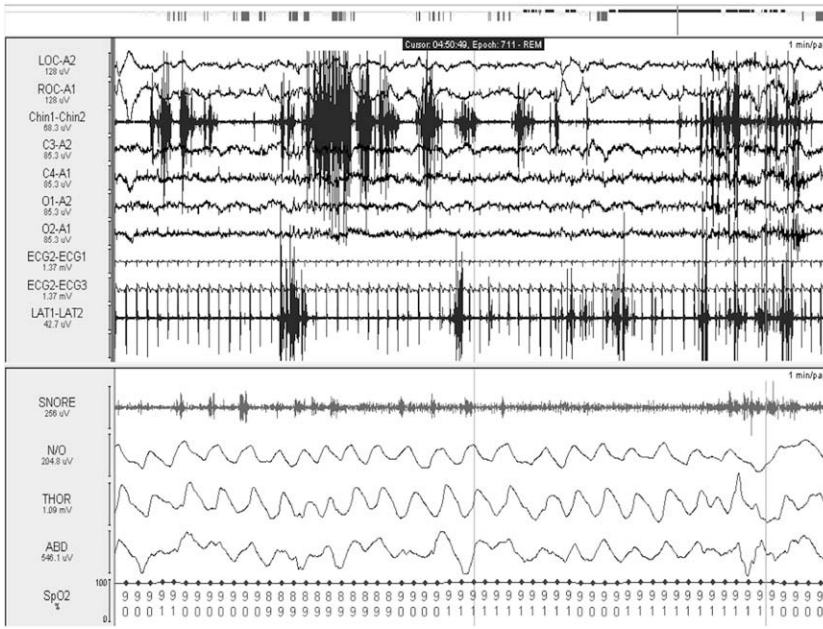

Fig. 2. Example of a 60-second epoch from a diagnostic PSG. Channels are as follows: EOG (left, LOC-A2; right, ROC-A1), chin EMG, EEG (left central, right central, left occipital, right occipital), two EKG channels, limb EMG (LAT), snore channel, nasal-oral airflow, respiratory effort (thoracic, abdominal) and oxygen saturation (SpO2). The patient was a 77-year-old man who was referred to the sleep disorders clinic for evaluation of recurrent violent nighttime awakenings. (*Data from* Avidan AY, Zee P, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 187–201.)

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 pain[19,20] 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, psychophysiologic 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 insomnia[30,32] 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,

Table 2
Food and Drug Administration–approved pharmacologic treatments of insomnia

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

Data from Silber MH. Chronic insomnia. N Engl J Med 2005;353:803–10.

and temazepam, and nonbenzodiazepine hypnotics, including zolpidem, zolpidem tartrate, zaleplon, and eszipiclone.[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.[13] The nonbenzodiazepine hypnotics have less potential for abuse, tolerance, or withdrawal,[35] but may be associated with increased propensity for rebound insomnia and amnestic reactions in higher doses.[14]

Melatonin receptor agonists, such as ramelteon, are a newer class of Food and Drug Administration (FDA)–approved agents for sleep-onset insomnia.[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.[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.[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.[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.

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.[5] 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.[6,39–41] 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.[5,42] 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.[43]

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.[44] Risk factors include increased age,

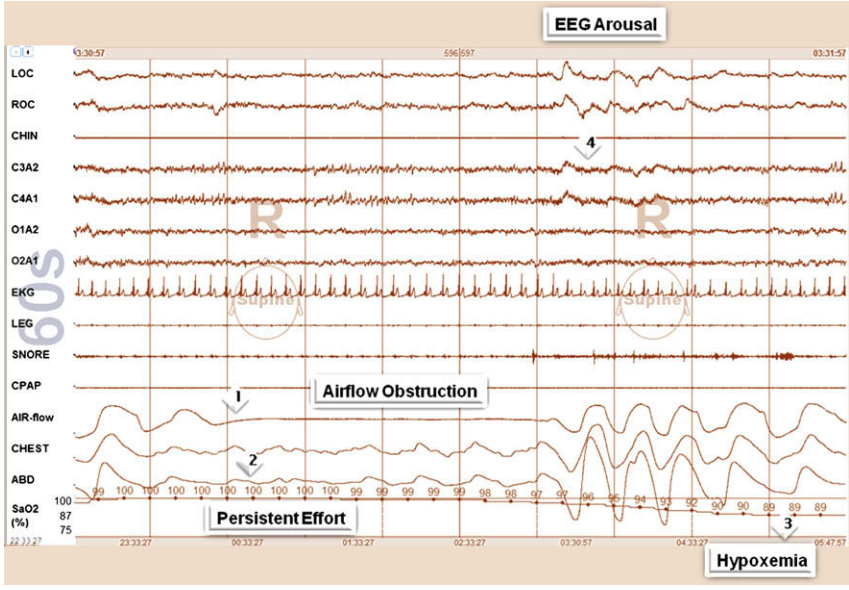

Fig. 3. A 60-second epoch (recorded during stage Rapid Eye Movement (REM) sleep) from a diagnostic polysomnogram of a older man with a history of pauses in his breathing, snoring and excessive daytime somnolence previously admitted to the stroke unit with left hemiparesis and right middle cerebral artery 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 cahnnel is inactive.

male gender, obesity, and high cholesterol.[45] Snoring is also associated with an increased OSA risk, possibly related to snoring-induced pharyngeal edema and inflammation.[46] Sleep-disordered breathing is increased among older adults (mean age of 76 years old), with an estimated prevalence of 24% to 26%.[47] Among older adults, OSA with daytime sleepiness can cause significant cognitive difficulties, particularly in tests of attention.[48] Treatment with CPAP is effective in treating the cognitive and cardiovascular sequelae of OSA in the older population.[49]

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.[42] Patients who have craniofacial structural problems may be candidates for oral appliances, such as mandibular advancement devices.[42]

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.[50] The cardiovascular complications of OSA may also diminish.[50] 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.[51] 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%.[52] The reasons for this are multifactorial and may include physical side effects, such as nasal stuffiness, and psychologic obstacles.[52] The physical side effects can be ameliorated somewhat by use of heated humidification, nasal sprays, and correctly fitting the mask.[42]

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.[42,53–55] 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.[5,56–58] 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.[59] 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.[5,58]

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.[5] The prevalence ranges from as low as 0.002% in Israel to 0.15% in Japan.[5,58] The disease may present at any age but is typically diagnosed before age 25. Men are slightly more likely to be affected than women.[5]

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.[5,56] Specific autoantibody markers for narcolepsy have not yet been found, however.[60]

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.[61,62] 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.[56] 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.[56] Although sodium oxybate is the only approved medication for cataplexy in the United States, tricyclic antidepressants (TCAs), such as clomipramine, have

Table 3
Treatment options for narcolepsy and cataplexy

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

Abbreviation: EDS, excessive daytime sleepiness.
Data from Wise MS, Arand DL, Auger RR, et al. Treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30(12):1712–27.

been used to treat cataplexy successfully for decades. TCAs may cause more severe rebound cataplexy if abruptly discontinued, however.[56,57] More recently serotonin and norepinephrine reuptake inhibitors have also been used for cataplexy, including fluoxetine and venlafaxine.[57,63] Nonpharmacologic therapy using regular bedtimes and strategically timed power naps may also improve alertness.[58,64]

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.[5,65–67]

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.[66] 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.[66] 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.[66]

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.[78] 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 quiescegenic 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 4
Treatment of restless legs syndrome

Drug	Dose	Risks
Iron		
Ferrous sulfate	325 mg bid to tid Recommended for serum ferritin <50 μg	GI side effects: constipation. Role in treatment under current investigation
Dopamine agonists		
Pramipexole	0.125–0.5 mg, 2–3 h before bedtime. Start low and increase slowly[a]	Severe sleepiness, nausea, vomiting, sleep attacks, rare compulsive gambling, hallucinations, orthostatic hypotension
Ropinirole	0.25–2 mg 1–2 h before bedtime[a]	Severe sleepiness, nausea, vomiting, sleep attacks, rare compulsive gambling, hallucinations, orthostatic hypotension
Dopaminergic agents		
Levodopa/carbidopa	25/200 mg: 1/2 tab to 3 tabs 30 min before bedtime.	Nausea, sleepiness, augmentation of daytime symptoms, insomnia, sleepiness, gastrointestinal disturbances
Anticonvulsants		
Gabapentin	300–2700 mg/d divided tid	Daytime sleepiness, nausea
Benzodiazepines		
Clonazepam	0.125–0.5 mg half hour before bedtime	Nausea, sedation, dizziness
Clonidine		
Catapres	0.1 mg bidMay be helpful in patients who have hypertension	Dry mouth, drowsiness, constipation, sedation, weakness, depression (1%), hypotension
Opioids		
Propoxyphene and acetaminophen Propoxyphene Codeine	300 mg/d 65–135 mg at bedtime 30 mg	Nausea, vomiting, restlessness, constipation. Addiction, tolerance may be possible

[a] Only FDA-approved drugs for RLS as of August, 2008.
Data from Avidan AY, Zee P, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 98–136.

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.[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**).[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.[91,100] Second-line medications include gabapentin, benzodiazepines, clonidine, or opiates, such as oxycodone.[69] Patients who have iron deficiency anemia–associated RLS should also be treated with iron supplements as adjunctive therapy.[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

1. Thorpy MJ. Approach to the patient with a sleep complaint. Semin Neurol 2004; 24(3):225–35.
2. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39(6):411–8.
3. Lockley SW, Barger LK, Ayas NT, et al. Effects of health care provider work hours and sleep deprivation on safety and performance. Jt Comm J Qual Patient Saf 2007;33(11 Suppl):7–18.
4. Copinschi G. Metabolic and endocrine effects of sleep deprivation. Essent Psychopharmacol 2005;6(6):341–7.
5. American Academy of Sleep Medicine, A. The international classification of sleep disorders. In: Sateia M, editor. Diagnostic and coding manual. 2nd edition. Westchester (IL): American Academy of Sleep Medicine; 2005. p. 1–297.
6. Hailey D, Tran K, Dales R, et al. Recommendations and supporting evidence in guidelines for referral of patients to sleep laboratories. Sleep Med Rev 2006; 10(4):287–99.
7. Bae C, Avidan A. Evaluation and testing of the sleepy patient. In: Smith HR, Comella CL, Birgit H, editors. Sleep medicine. Cambridge (UK): Cambridge University Press; 2008. p. 25–46.
8. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540–5.
9. Boeve BF, Silber MH, Ferman TJ. REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol 2004; 17(3):146–57.
10. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 1996;46(2):388–93.
11. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005; 28(1):113–21.

12. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 2005;28(4):499–521.
13. Silber M. Insomnia. Continuum Lifelong Learning Neurol 2007;13(3):85–100.
14. Benca RM. Insomnia. In: Avidan AY, Zee PC, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 36–69.
15. National Institutes of Health State of the Science Conference statement on manifestations and management of chronic insomnia in adults, June 13–15, 2005. Sleep 2005;28(9):1049–57.
16. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6(2):97–111.
17. Ohayon MM, Roth T. What are the contributing factors for insomnia in the general population? J Psychosom Res 2001;51(6):745–55.
18. Ohayon MM, Zulley J, Guilleminault C, et al. How age and daytime activities are related to insomnia in the general population: consequences for older people. J Am Geriatr Soc 2001;49(4):360–6.
19. Smith MT, Klick B, Kozachik S, et al. Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. Pain 2008;138(3):497–506.
20. Stiefel F, Stagno D. Management of insomnia in patients with chronic pain conditions. CNS Drugs 2004;18(5):285–96.
21. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med 2005;165(8):863–7.
22. Phillips B, Mannino DM. Do insomnia complaints cause hypertension or cardiovascular disease? J Clin Sleep Med 2007;3(5):489–94.
23. Sallinen M, Holm J, Hirvonen K, et al. Recovery of cognitive performance from sleep debt: do a short rest pause and a single recovery night help? Chronobiol Int 2008;25(2):279–96.
24. Pj H. Primary insomnia. 2003.
25. Fetveit A, Straand J, Bjorvatn B. Sleep disturbances in an arctic population: The Tromso Study. BMC Health Serv Res 2008;8:117–25.
26. Nofzinger EA, Buysse DJ, Germain A, et al. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161(11):2126–8.
27. Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. Psychosom Med 2003;65(2):259–67.
28. Durmer J, Chervin R. Pediatric sleep medicine. Continuum Lifelong Learning Neurol 2007;13(3):153–200.
29. Rybarczyk B, Stepanski E, Fogg L, et al. A placebo-controlled test of cognitive-behavioral therapy for comorbid insomnia in older adults. J Consult Clin Psychol 2005;73(6):1164–74.
30. Sivertsen B, Omvik S, Pallesen S, et al. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. JAMA 2006;295(24):2851–8.
31. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. Health Psychol 2006;25(1):3–14.
32. Edinger JD, Means MK. Cognitive-behavioral therapy for primary insomnia. Clin Psychol Rev 2005;25(5):539–58.
33. Wu R, Bao J, Zhang C, et al. Comparison of sleep condition and sleep-related psychological activity after cognitive-behavior and pharmacological therapy for chronic insomnia. Psychother Psychosom 2006;75(4):220–8.

34. Edinger JD, Wohlgemuth WK, Radtke RA, et al. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. Sleep 2007; 30(2):203–12.
35. Lieberman JA. Update on the safety considerations in the management of insomnia with hypnotics: incorporating modified-release formulations into primary care. Prim Care Companion J Clin Psychiatry 2007;9(1):25–31.
36. Zammit G, Erman M, Wang-Weigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med 2007; 3(5):495–504.
37. Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med 2005;20(12):1151–8.
38. Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 2006;332(7538):385–93.
39. Banno K, Kryger MH. Sleep apnea: clinical investigations in humans. Sleep Med 2007;8(4):400–26.
40. White DP. Sleep apnea. Proc Am Thorac Soc 2006;3(1):124–8.
41. Tabba MK, Johnson JC. Obstructive sleep apnea: a practical review. Mo Med 2006;103(5):509–13.
42. Chan A, Kushida C. Sleep-disordered breathing. Continuum Lifelong Learning Neurol 2007;13(3):139–52.
43. Sewell-Scheuermann S, Phillips B. Sleep-disordered breathing. In: Avidan AY, Zee PC, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 13–35.
44. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230–5.
45. Tishler PV, Larkin EK, Schluchter MD, et al. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. JAMA 2003;289(17):2230–7.
46. Hudgel DW. Mechanisms of obstructive sleep apnea. Chest 1992;101(2):541–9.
47. Mehra R, Stone KL, Blackwell T, et al. Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. J Am Geriatr Soc 2007;55(9):1356–64.
48. Alchanatis M, Zias N, Deligiorgis N, et al. Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. Sleep Breath 2007;12(1):17–24.
49. Weaver TE, Chasens ER. Continuous positive airway pressure treatment for sleep apnea in older adults. Sleep Med Rev 2007;11(2):99–111.
50. Guilleminault C, Abad VC. Obstructive sleep apnea syndromes. Med Clin North Am 2004;88:611–30.
51. Lavie L. Sleep-disordered breathing and cerebrovascular disease: a mechanistic approach. Neurol Clin 2005;23(4):1059–75.
52. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008;5(2):173–8.
53. Sundaram S, Bridgman SA, Lim J, et al. Surgery for obstructive sleep apnoea. Cochrane Database Syst Rev 2005;(4):CD001004.
54. Sher A, Goldberg A. Upper airway surgery for obstructive sleep apnea. Sleep apnea pathogenesis diagnosis and treatment. In: Pack A, editor. Sleep apnea. New York: Marcel Dekker; 2002. p. 575–605.

55. Pillar G, Schnall R, Peled R, et al. Surgical treatment of sleep apnea syndrome. Isr J Med Sci 1996;32(9):710–5.
56. Thorpy MJ. Narcolepsy. Continuum Lifelong Learning Neurol 2007;13(3):101–14.
57. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet 2007; 369(9560):499–511.
58. Hoban T, Chervin R. Hypersomnia and narcolepsy. In: Avidan A, Zee PC, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 70–97.
59. The international classification of sleep disorders pocket version: diagnostic & coding manual. 2nd editon. West (IL): American Academy of Sleep Medicine; 2006.
60. Black JL 3rd. Narcolepsy: a review of evidence for autoimmune diathesis. Int Rev Psychiatry 2005;17(6):461–9.
61. Broughton RJ, Fleming JA, George CA, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 1997;49(2):444–51.
62. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology 2000;54(5):1166–75.
63. Thorpy M. Therapeutic advances in narcolepsy. Sleep Med 2007;8(4):427–40.
64. Wise MS, Arand DL, Auger RR, et al. Treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30(12):1712–27.
65. Okawa M, Uchiyama M. Circadian rhythm sleep disorders: characteristics and entrainment pathology in delayed sleep phase and non-24-h sleep-wake syndrome. Sleep Med Rev 2007;11(6):485–96.
66. Lu B, Manthena P, Zee PC. Circadian rhythm sleep disorders. In: Avidan A, Zee PC, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 137–64.
67. Reid KJ, Zee PC. Circadian rhythm disorders. Semin Neurol 2004;24(3):315–25.
68. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. Sleep 2007;30(11):1445–59.
69. Avidan A. Motor disorders of sleep and parasomnias. In: Avidan A, Zee PC, editors. Handbook of sleep medicine. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 98–136.
70. Vaughn BV, D'Cruz ON. Parasomnias and other nocturnal events. American Academy of Neurology Continuum: lifelong learning in neurology. Sleep Disorders 2007;13(3):225–47.
71. Zaiwalla Z. Parasomnias. Clin Med 2005;5(2):109–12.
72. Lee-Chiong TL Jr. Parasomnias and other sleep-related movement disorders. Prim Care 2005;32(2):415–34.
73. Ferini-Strambi L, Fantini ML, Zucconi M, et al. REM sleep behaviour disorder. Neurol Sci 2005;26(Suppl 3):s186–92.
74. Mahowald MW, Bornemann MC, Schenck CH. Parasomnias. Semin Neurol 2004; 24(3):283–92.
75. Farid M, Kushida CA. Non-rapid eye movement parasomnias. Curr Treat Options Neurol 2004;6(4):331–7.
76. Leo G. Parasomnias. WMJ 2003;102(1):32–5.
77. Sheldon SH. Parasomnias in childhood. Pediatr Clin North Am 2004;51(1):69–88, vi.
78. Ferini-Strambi L, Zucconi M. REM sleep behavior disorder. Clin Neurophysiol 2000;111(Suppl 2):S136–40.

79. Matsurnoto M, Mutoh F, Naoe H, et al. The effects of imipramine on REM sleep behavior disorder in 3 cases. Sleep Res 1991;20A:351.
80. Nash JR, Wilson SJ, Potokar JP, et al. Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. Neurology 2003;61(8):1161.
81. Stolz SE, Aldrich MS. REM sleep behavior disorder associated with caffeine abuse. Sleep Res 1991;20:341.
82. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med 2003;4(4):281–4.
83. Boeve B. Melatonin for treatment of REM sleep behavior disorder: response in 8 patients. Sleep 2001;24(Suppl):A35.
84. Ringman JM, Simmons JH. Treatment of REM sleep behavior disorder with donepezil: a report of three cases. Neurology 2000;55(6):870–1.
85. Bamford CR. Carbamazepine in REM sleep behavior disorder. Sleep 1993; 16(1):33–4.
86. Walters AS. Restless legs syndrome and periodic limb movements in sleep. American Academy of Neurology Continuum: lifelong learning in neurology. Sleep Disorders 2007;13(3):115–38.
87. Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. Lancet Neurol 2005;4(8):465–75.
88. Benes H, Walters AS, Allen RP, et al. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. Mov Disord 2007; 22(Suppl 18):S401–8.
89. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4(2):101–19.
90. Rama AN, Kushida CA. Restless legs syndrome and periodic limb movement disorder. Med Clin North Am 2004;88(3):653–67, viii.
91. Lesage S, Hening WA. The restless legs syndrome and periodic limb movement disorder: a review of management. Semin Neurol 2004;24(3):249–59.
92. Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006;67(6):1034–9.
93. Littner MR, Kushida C, Anderson WM, et al. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27(3):557–9.
94. Lesage S, Earley CJ. Restless legs syndrome. Curr Treat Options Neurol 2004; 6(3):209–19.
95. Hening WA, Allen RP, Earley CJ, et al. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004; 27(3):560–83.
96. Cheer SM, Bang LM, Keating GM. Ropinirole: for the treatment of restless legs syndrome. CNS Drugs 2004;18(11):747–54 [discussion 755–6].
97. Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep 2004;27(5):907–14.
98. Adler CH, Hauser RA, Sethi K, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology 2004;62(8):1405–7.
99. Wetter TC, Winkelmann J, Eisensehr I. Current treatment options for restless legs syndrome. Expert Opin Pharmacother 2003;4(10):1727–38.
100. Trenkwalder C, Hogl B, Benes H, et al. Augmentation in restless legs syndrome is associated with low ferritin. Sleep Med 2007;9(5):572–4.