Sleep disorders
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Introduction

This article includes discussion of sleep disorders, circadian rhythm sleep disorders, insomnia associated with intrinsic sleep disorders, sleep disorders presenting with altered breathing during sleep, sleep disorders presenting with altered sensation during arousals, sleep disorders presenting with complex movements during sleep, sleep disorders presenting with excessive sleepiness, sleep disorders presenting with insomnia, and sleep disorders presenting with simple movements during sleep. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

The author offers an overview of the sleep disorders. This area of medicine has experienced a quasi-explosive expansion since the early development of clinical sleep laboratories in the 1970s. Sleep medicine oversees conditions as common as insomnia, restless legs syndrome, and sleep apnea, which have emerged as important risk factors for vascular disease and other ailments such as diabetes. New information points to moderate to severe sleep apnea as a factor in cognitive decline. Sleep neurology also covers less common but equally socially destructive disorders such as narcolepsy and the circadian dysrhythmias. Many neurologic disorders have associated sleep dysfunctions. The study of sleep physiology and pathophysiology is a window to the function of the brain. Overall successful clinical management of sleep disorders, whether insomnias or hypersomnias, improves the quality of life. This article discusses the most salient innovations and discoveries in sleep medicine that have occurred during the preceding year.

Key points

• Sleep medicine oversees conditions as common as insomnia, restless legs syndrome, and sleep apnea that reduce the quality of life and diminish the health of the individual.
• Some of these conditions have emerged as important risk factors for vascular disease, diabetes, and cognitive decline.
• It also covers less common but equally socially destructive disorders such as narcolepsy and the circadian dysrhythmias.
• Many neurologic disorders have associated sleep dysfunctions.
• The study of sleep physiology and pathophysiology is a window to the function of the brain.
• Successful clinical management of sleep disorders, whether insomnias, hypersomnias, parasomnias, or breathing disorders, improves the quality of life and ameliorates the health of the individual.

Historical note and terminology

Although sleep is a universal experience, it was not studied systematically by scientists and physicians until the 20th century. Prior to the discovery of brain electrical activity, sleep was often assumed to be a passive response to reduced cerebral stimulation associated with mental and cerebral inactivity. Aristotle believed that the condition of sleep was initiated by warm vapors from the stomach (Horne 1988). Others attributed sleep to the effects of vascular congestion or anemia or to the buildup of “hypnotoxins.”

Berger’s demonstration of changes in the electroencephalogram (EEG) during sleep followed by the sleep-EEG studies of Loomis and colleagues provided the first definite evidence that the brain is not passive during sleep (Berger 1930; Loomis et al 1937). Studies of encephalitis lethargica by von Economo, of hypothalamic and thalamic stimulation by Hess, and of the reticular activating system by Moruzzi and Magoun provided major advances in the understanding of the neuroanatomical substrate of sleep and wakefulness (von Economo 1930; Hess 1944; Moruzzi and Magoun 1949). The discoveries of rapid eye movement (REM) sleep (Aserinsky and Kleitman 1953) and repetitive cycles of REM and NREM sleep throughout the night (Dement and Kleitman 1957) led to a new view of sleep as an active process with distinctive neurophysiological substrates underlying the 2 major sleep states.
Physicians have known for centuries that sleep disturbance is often a sign of disease, but the recognition that primary sleep disorders are common, serious, and often treatable has occurred mainly in the second half of the 20th century. Narcolepsy, recognized in the 19th century, was often considered a form of epilepsy or a psychiatric disturbance until the discovery of its association with abnormal REM sleep (Rechtschaffen et al 1963; Takahashi and Jimbo 1963). This discovery made narcolepsy the first identified primary sleep disorder; that is, a disorder associated with abnormalities of the sleep process and associated primarily with sleep-related symptoms.

In the mid-1960s, 2 other discoveries led to the recognition that sleep could facilitate the appearance of specific disorders. The first was the identification of abnormal breathing patterns during sleep in association with obesity (Pickwickian syndrome) (Gastaut et al 1965; Jung and Kuhlo 1965); the second was the discovery of regular recurring patterns of leg movements during sleep (Lugaresi et al 1966), now called periodic limb movements of sleep. Further study of breathing during sleep led to the recognition of the importance of upper airway occlusion as a primary cause of sleep-related breathing disturbance (Sadoul and Lugaresi 1972).

In the 1970s, the first sleep clinics appeared devoted specifically to diagnosis and treatment of a broad range of sleep disorders. The Association of Sleep Disorders Centers, organized in 1975, provided a focus for development of the field of sleep disorders medicine. Subsequent major events included the publication of Sleep, the first journal devoted specifically to sleep disorders medicine. As the breadth of the field emerged, it became apparent that a nosology devoted to sleep disorders was required. The Association of Sleep Disorders Centers published the first classification of sleep disorders in 1979 (Association of Sleep Disorders Centers 1979). A more comprehensive classification was published by the American Sleep Disorders Association in 1990 as the International Classification of Sleep Disorders, and revised in 2000 (American Sleep Disorders Association 2000). It was updated in 2005 by the American Academy of Sleep Medicine and again in 2014 (American Academy of Sleep Medicine 2014) (Table 1). The first board certification exam on sleep medicine offered by authorized member boards of the American Board of Medical Specialties (American Board of Psychiatry and Neurology, American Board of Family Medicine, American Board of Internal Medicine, American Board of Otolaryngology and American Board of Pediatrics) took place in November 2007 and will be given every 2 years. Waivers of formal fellowship training to apply for the new exam expired in 2011.

Table 1. International Classification of Sleep Disorders

1. Insomnia
2. Sleep-related breathing disorders
3. Central disorders of hypersomnolence
4. Circadian rhythm sleep-wake disorders
5. Parasomnias
6. Sleep-related movement disorders
7. Other sleep disorders

Appendix A: Sleep related medical and neurologic disorders
Appendix B: ICD-10-CM coding for substance-induced sleep disorders

Clinical manifestations

Presentation and course

Sleep complaints generally fall into 6 major categories: (1) insomnia, (2) excessive somnolence, (3) snoring and sleep breathing difficulties, (4) sleep-wake disruption (circadian dysrhythmia), (5) bizarre sleep-related behaviors (parasomnias), and (6) sleep-related movement disorders. Insomnia includes complaints of difficulty falling asleep, staying asleep, awakening too early, and a feeling that sleep has not provided the usual sense of restoration. Excessive daytime sleepiness refers to uncontrollable drowsiness and unwanted sleep episodes during waking hours. The term hypersomnia should be restricted to conditions of excessive sleep duration. Circadian dysrhythmias refer to disorders of timing of the sleep-wake pattern with the night-day cycle. Parasomnias are defined as undesirable physical phenomena that occur primarily during sleep. A particular sleep disorder may be associated with 1 or more of these major categories of symptoms. For example, obstructive sleep apnea may be associated with restless sleep and frequent awakenings (insomnia); choking, gasping, and mumbling during sleep (parasomnia); and irresistible drowsiness (hypersomnia).

The chief complaint provides a focus for assessing the patient’s concerns and for eliciting the history. Information from the bed partner or other observers must often be obtained, as most patients are unaware of the frequency and
severity of snoring and cannot describe leg jerks, twitches, sleep walking, or violent behavior during sleep. The duration of the complaint and the circumstances at the onset of sleep difficulties are important pieces of information.

The daily schedule, including time of awakening and going to bed; time of naps; time of meals and social activities; and time and use of caffeine, alcohol, tobacco, and prescription and over-the-counter medications may point to particular sleep disorders. The bedtime routine and the method of awakening (i.e., spontaneous, with an alarm, or by a family member) should be determined, and the sleep schedule during weekdays, weekends, or days off from work or school should be compared. The sleeping environment may play a role in sleep disruption; excessive noise, extreme temperatures, or an uncomfortable bed may be significant factors. The relationship between sleep disturbance and medical illness should be assessed as such disorders as arthritis, asthma, heart disease, gastroesophageal reflux, and psychiatric disorders are commonly associated with disturbed sleep.

Patients with excessive sleepiness may describe drowsiness, increased need for sleep, or irresistible daytime sleep episodes. Others have little awareness of their daytime sleep episodes or believe that they represent normal sleep patterns. For some patients, falling asleep while driving or in other dangerous situations is the impetus that leads to evaluation. Mild sleepiness is most often apparent during the afternoon in quiet, boring situations; with more severe sleepiness, the patient may report falling asleep while eating, in conversation, or while standing. Symptoms associated with sleepiness provide important clues to diagnosis. Loud snoring and witnessed apneas during sleep strongly point to obstructive sleep apnea syndrome. Bilateral muscle weakness in conjunction with laughter or other emotions is characteristic of cataplexy, which in combination with excessive sleepiness, is virtually diagnostic of narcolepsy.

Patients who complain of nocturnal insomnia and daytime sleepiness may have circadian rhythm sleep disorders. For example, difficulty falling asleep at night followed by normal sleep and difficulty waking up in the morning may be due to delayed sleep phase syndrome.

Patients with parasomnias may complain of a variety of nocturnal sensations or exhibit bizarre movements, behaviors, or bodily events. Some patients are entirely unaware of the nighttime activity, and a history from the bed partner or other observers is necessary. Some of the more distressing symptoms include nocturnal urinary incontinence (enuresis), shouting or screaming, and violent behavior. Patients may be particularly concerned about the possibility that serious medical illnesses are responsible for nighttime episodes of chest pain, gasping or choking, and palpitations. Furthermore, other patients are rightly distressed about possible nocturnal accidents or injuries to the bedmate.

**Prognosis and complications**

The prognosis depends on the particular sleep disorder. Therapeutic CPAP administration reduced mean arterial blood pressure by 3.3 mm Hg in a controlled study of hypertensive patients with moderate or severe obstructive sleep disordered breathing (Pepperell et al 2002). The drop was observed after 3 to 4 weeks of continuous treatment, affecting systolic and diastolic pressures and during periods of being both asleep and awake. Patients with most severe sleep apnea disorder benefited the most, particularly if they were taking drug treatment for hypertension. The extrapolation of these results suggests that a fall of 3.3 mm Hg in blood pressure would be expected to be associated with a stroke risk reduction of 20% and a coronary heart disease event risk reduction of 15%. The estimated combined stroke and coronary event risk for moderate and severe sleep disordered breathing is 3% per year (Kiely and McNicholas 2000). Up to 1.5% of adult men have sleep-disordered breathing of this severity (Stradling et al 2000). Therefore, effective treatment of sleep disordered breathing could prevent 12,600 vascular events in men per year in the United States. Such reduction is comparable to that seen in the pharmacological treatment for control of hypertension. In the study by Becker and colleagues, effective CPAP treatment in patients with moderate or severe sleep apnea or hypopnea disorder led to a 10 mm Hg drop in mean arterial blood pressure (Becker et al 2003).

There is a strong association between sleep apnea, as measured by the sleep apnea-hypopnea index, and traffic accidents (Teran-Santos et al 1999). In patients with an apnea-hypopnea index of 10 or higher, the odds ratio for having a traffic accident is 6.3 (2.4 to 16.2 confidence interval). Consumption of alcohol increases the odds even further. Patients with narcolepsy and other forms of excessive daytime sleepiness also have a higher chance of being involved in automobile accidents.

In untreated men with severe obstructive sleep apnea-hypopnea (AHI > 30) the risk of fatal and nonfatal cardiovascular (MI, acute coronary insufficiency, and stroke) events is increased as compared to healthy subjects (fatal
risk, OR 2.87, 95%CI 1.17-7.51; nonfatal risk, OR 3.17, 95%CI 1.12-7.51) (Marin et al 2005). Patients with obstructive sleep apnea have a peak in sudden death from cardiac causes during the sleeping hours (midnight to 6 AM). People without obstructive sleep apnea have a nadir in sudden death from cardiac causes during the same period of time (Gami et al 2005). Evidence is mounting that acute stroke patients have a high prevalence of sleep apnea (Culebras 2009), and when severe, it modifies cerebral blood flow and may facilitate neurologic deterioration. This has been termed “reversed Robin Hood syndrome” (Alexandrov et al 2007). Prompt application of noninvasive ventilation may reduce the risk of neurologic deterioration in patients with acute stroke and sleep apnea, but further clinical research is required.

Abnormal sleep patterns have a distinct impact on endocrine function in general and glucose metabolism in particular. Experimentally induced sleep deprivation in young men is associated with glucose intolerance as well as with other alterations of endocrine function and metabolic regulation (Spiegel et al 1999). Hypercortisolism has been observed in idiopathic hypersomnia, and hypothalamic-pituitary axis relative activation has been linked with chronic insomnia (Vgontzas et al 1999). Provocative research associates sleep alterations and diabetes type II in men and in women but surprisingly finds evidence of a link only in women (Tuomilehto et al 2008).

REM sleep behavior disorder may herald the onset of alpha-synucleinopathies (Parkinson disease, multiple system atrophy, and dementia with Lewy bodies) by as many as 50 years (Claassen et al 2010).

Parasomnia overlap disorder is emerging as an important neurologic condition (Howell and Shenck 2010). Parasomnia overlap disorder occurs when patients demonstrate features of both NREM parasomnias and REM sleep behavior disorder (Schenck et al 1997). ICSD-2 defines parasomnia overlap disorder as a combination of REM sleep behavior disorder and a disorder of arousal (sleep walking, confusional arousal, or sleep terror). Polysomnography in parasomnia overlap disorder typically demonstrates NREM sleep instability in combination with REM sleep without atonia, at times with dream enactment behaviors. One third of patients with parasomnia overlap disorder have brainstem lesions and, therefore, formal neurologic evaluation is necessary, particularly if the results of the neurologic exam are abnormal. Treatment of parasomnia overlap disorder should be focused on resolving comorbid conditions that fragment sleep, such as sleep-disordered breathing, and elimination of suspected precipitating pharmacology. Clonazepam is often effective, particularly for patients with violent dream enactment behavior.

Cognitive decline in patients with vascular dementia and neurodegenerative disease may be accelerated by uncontrolled moderate to severe car apnea (Osorio et al 2015; Ramos et al 2015). There is preliminary evidence that treatment with CPAP may delay progression of cognitive impairment (Ramos et al 2015). Frequent snoring (β = -29; p = 0.0007), severe daytime sleepiness (β = -29; p = 0.05), and long sleep duration (β = -29; p = 0.04) predicted decline in executive function, adjusting for demographic characteristics, in the Northern Manhattan Study (Ramos et al 2016).

Clinical vignette

A 26-year-old man fell asleep in the dentist’s chair. He had a history of excessive sleepiness during daytime hours which he attributed to his poor nocturnal sleep. His work productivity had declined and he had been cited to appear in court because of several unexplained car accidents. His family physician had requested an EEG as part of the evaluation of a sudden fall at a party where people were cracking jokes. The patient’s father had been killed in an automobile accident and the presumption was that he had fallen asleep at the wheel.

The physical and neurologic exams were normal but the EEG showed abundant sleep with possible REM activity and the interpreter suggested performing nocturnal polysomnography. The overnight study showed short onset REM sleep latency of 20 minutes and 30% REM sleep. Nocturnal sleep was fragmented because of arousals and awakenings. The multiple sleep latency test showed a short sleep latency of 3 minutes, short onset REM sleep latency of 1 minute, and REM sleep in 4 out of 4 naps. A diagnosis of narcolepsy with possible cataplexy was made.

The patient was counseled by the treating sleep physician who recommended 2 daytime naps of 15 minutes duration each, at 13:00 after lunch and at 17:00 when the patient arrived home from work. He also recommended a regimented sleep hygiene and extended a prescription for modafinil to take 200 mg in the morning. He advised the patient to call his office if modafinil showed only partial efficacy and to report more episodes of falling asleep were these to occur. Three months later the patient reported improved daytime alertness and increased work productivity. There had been no more car accidents or near-misses. The treating physician kept open the possibility of cataplexy and advised the
patient to report any incidents of muscle weakness precipitated by emotions. The physician discussed the administration of sodium oxybate with the patient, for future reference.

**Biological basis**

**Etiology and pathogenesis**

The etiology of sleep disorders is a function of the individual disorder. Narcolepsy research suggests an important role for the hypothalamic peptide neurotransmitters hypocretin 1 and 2 (De Lecea et al 1998) also called orexin A and B. Experimental studies have shown that narcolepsy is caused in dogs by a deletion in the hypocretin receptor-2 gene (Lin et al 1999). Another group of investigators showed that hypocretin knockout mutant mice developed REM sleep or cataplexy while awake (Chemelli et al 1999). These discoveries led to the hypothesis that reduced production of hypocretin in cells of the perifornical area in the lateral and posterior hypothalamus could underlie most cases of human narcolepsy. Further observations in humans support the notion that narcolepsy is an acquired disorder and caused by destruction of cells in the hypothalamus (Silber and Rye 2001). In a study to evaluate the possible association between Pandemrix® vaccination and narcolepsy in Norway, 58 vaccinated children and adolescents (35 girls, 23 boys) aged 4 to 19 years (mean age 10.5 years) were diagnosed as new cases of confirmed narcolepsy, most within 6 months after vaccination (Heier et al 2013). Thirty-seven patients who were analyzed had tissue type HLADQB1*0602. The authors concluded that there is a significantly increased risk for narcolepsy with cataplexy (P<.0001) and reduced CSF hypocretin levels in vaccinated children during the first year after Pandemrix® vaccination, particularly in genetically predisposed subjects.

Genetic involvement may contribute to disorders such as circadian rhythm disorders (genetic polymorphism in gene hPer2 and hPer3), restless legs syndrome, periodic limb movements, and congenital central hypoventilation (PHOX2B gene) (Amiel et al 2003; Archer et al 2003; Stefansson et al 2007; Trotti et al 2008).

The pathogenesis and pathophysiology of sleep disorders are a function of the individual disorder.

Sleep-related obstruction to the flow of air in obese patients with a small oropharynx remains the most common mechanism for development of sleep apnea. However, other pathogenetic factors, mostly central in origin, are at play potentiating a clinically significant expression and disease. There is an intimate relationship between the autonomic nervous system and sleep. The concept of a state-dependent regulation of the autonomic nervous system has been addressed. Lugaresi and colleagues were the first to describe intense changes in systemic and pulmonary blood pressure associated with apneas and the renewal of breathing in sleep apnea patients (Lugaresi et al 1972). This discovery opened a line of investigation that promises to uncover major pathophysiologic interactions between the sleep circuits and the autonomic nervous system involving thermoregulation, respiratory functions, cardiovascular regulation, and hormonal secretions (Cortelli 2007).

Chemoreflex-mediated sleep apnea is a new area of inquiry (Thomas 2009). Central sleep apnea may occasionally occur in patients with obstructive sleep apnea during titration with a continuous positive airway pressure (CPAP) device. In a large retrospective study of 1286 patients with a diagnosis of obstructive sleep apnea, 6.5% had CPAP-related central sleep apnea. CPAP-emergent central sleep apnea was generally transitory and was eliminated within 8 weeks after CPAP therapy. The prevalence of CPAP-persistent central sleep apnea was about 1.5%. Severity of obstructive sleep apnea, a central apnea index of 5 or greater per hour, and use of opioids were potential risk factors (Javaheri 2009).

Chronic intermittent hypoxia may damage the endothelium and trigger the release of proinflammatory factors, plasma cytokines, tumor necrosis factor-alpha, and interleukin-6. Furthermore, chronic intermittent hypoxia may lead to vascular dysfunction by increasing endothelin, increasing neurovascular oxidative stress, decreasing vascular neuromuscular reserve, decreasing vascular reactivity, and increasing susceptibility to injury (Iadecola 2011).

In pregnant women with sleep apnea, placental hypoxia may precipitate a cascade of active factors from the placenta that generate profound effects on the maternal cardiovascular system causing hypertension, endothelial dysfunction, and preeclampsia.

Central dopamine metabolism and reduced iron stores, in a pattern that suggests that the homeostatic control of iron is altered, have been associated with restless legs syndrome and periodic limb movements (Satija and Ondo 2008). Alterations of the dopaminergic system also underlie REM sleep behavior disorder (RSBD), a REM sleep parasomnia.
that causes patients to enact their dreams. RSBD may herald the onset of a synucleinopathy more than 10 years before its clinical expression. Patients with the idiopathic form of RSBD with decreased striatal dopamine transporters imaging, substantia nigra hyperechogenicity, and hyposmia have an increased short-term risk for developing the classical motor, dysautonomic, and cognitive symptoms of a synucleinopathy (Iranzo 2011).

Sleep disturbances after traumatic brain injury occur in 30% to 70% of individuals suffering from brain trauma (Ouellet et al 2004). Insomnia, fatigue, and sleepiness are the most frequent complaints after head injury. The 2 main types of traumatic brain injury leading to altered sleep involve contact and acceleration/deceleration injuries. Diagnosis of a sleep disorder after traumatic brain injury may include polysomnography, multiple sleep latency test, and actigraphy. Treatment is disorder specific and includes the use of medications, continuous positive airway pressure (or similar device), and behavioral modifications.

Psychiatric and behavioral disorders are frequently encountered in the differential diagnosis of primary sleep disorders. These include anxiety disorders, mood disorders, schizophrenia, and somatoform disorders.

Hypoxia, autonomic dysfunction with loss of autoregulation, blood pressure instability, and inflammation may decrease cerebral blood flow in the territory of medullary penetrating arteries that irrigate the periventricular white matter. Small vessel disease of the brain generally affecting the subcortical and periventricular white matter is common in patients with advanced sleep apnea, old age, comorbidities (ie, diabetes), COPD, and smoking (Cho et al 2013; Kim et al 2013). The subcortical white matter irrigated by long, small-caliber, medullary, terminal arteries is functionally a borderzone area highly vulnerable to changes in blood pressure, altered vascular autoregulation, and hypoxia. Advanced small vessel disease increasingly disconnects the thalamic core of the brain from the frontal cortex, provoking a clinical picture where cognitive decline is dominant (Román 2013). The end of the spectrum is characterized by subcortical dementia, gait disturbance, and urinary incontinence, a condition that neuropathologists callBinswanger disease.

**Epidemiology**

Sleep disorders are common (Partinen 1994). About one third of adults report insomnia occurring at least occasionally over the course of a year, and one half of them describe it as a serious problem. Twenty percent of adults in the United States use medication for insomnia in a given month (Bertisch et al 2014). Up to one fourth of young to middle-aged adults use alcohol or medications to help with sleep problems (Johnson et al 1998). Among the elderly, sleep disturbances are even more common and are often associated with poor physical health, heart disease, or depression (Newman et al 1997). All neurodegenerative disorders are associated with some form of sleep dysfunction. Particular mention should be made of Parkinson disease, a condition that provokes many manifestations of sleep dysfunction, whether insomnia, excessive daytime sleepiness, circadian dysrhythmia, or parasomnias.

Symptoms of sleep apnea occur in 2% to 4% of the working adult population in the United States (Young et al 1993). In selected subpopulations, the prevalence of sleep disordered breathing is even higher. For example, in a population of Canadian male grain workers, many of whom were overweight, the prevalence of sleep disordered breathing was estimated to be 25% (Keenan et al 1998). Sleep apnea syndrome of moderate to severe intensity affects 17% of 50 to 70-year-old men and 9% of 50 to 70-year-old women (Peppard et al 2013). Sleep disordered breathing is a risk factor for the development of systemic hypertension (Nieto et al 2000; Peppard et al 2000a), myocardial infarction, stroke (Marin et al 2005; Yaggi et al 2005; Culebras 2013), atrial fibrillation (Gami et al 2007), and other ailments such as diabetes (Idriss et al 2009). The condition is common in patients recovering from stroke and may affect the functional outcome of the rehabilitation process (Good et al 1996). Sleep disordered breathing may be a life-threatening disorder in patients with neuromuscular disorders (Culebras 2007a).

Cognitive impairment may be yet another long-term effect of uncontrolled sleep apnea. Among older women, those with sleep-disordered breathing compared with those without had an increased risk of developing cognitive impairment, according to a prospective sleep and cognition study of 298 women without dementia (mean age 82.3 years) who had overnight polysomnography performed (Yaffe et al 2011). Compared with the 193 women without sleep-disordered breathing, the 105 women (35.2%) with sleep-disordered breathing were more likely to develop mild cognitive impairment or dementia (31.1% [n = 60] vs. 44.8% [n = 47]; adjusted odds ratio [AOR] 1.85; 95% [CI] 1.11-3.08). Elevated oxygen desaturation index (≥15 events/hour) and high percentage of sleep time (>7%) in apnea or hypopnea (both measures of disordered breathing) were associated with risk of developing mild cognitive impairment or dementia (AOR 1.71 [95% CI 1.04-2.83] and AOR 2.04 [95% CI 1.10-3.78], respectively). The arousal index and
wake after sleep onset that measure sleep fragmentation were not associated with risk of cognitive impairment.

Partial sleep deprivation and disturbed sleep patterns are common in shift workers in most industrialized societies. Sleep disorders are also common problems in children, and most adolescents probably do not get enough sleep to maintain optimal daytime alertness (Ancoli-Israel 1997). The estimation has been made that 1500 fatal motor vehicle accidents per year in the United States are the consequence of falling asleep at the wheel (National Highway Traffic Safety Administration 1997).

Insomnia is rapidly emerging as a disorder with ample medical ramifications (Winkelman 2015). Clinical research suggests that adolescents with low sleep efficiency had a 4.0+/-1.2 mm Hg higher systolic blood pressure than other children (P<0.01), and the authors concluded that poor sleep quality is associated with prehypertension in healthy adolescents (Javaheri et al 2008). Insomnia, sleep fragmentation, and any kind of sleep deprivation in general may be associated with diabetes type 2 (Ayas et al 2003; Gottlieb et al 2005; Tuomilehto et al 2008).

During the third trimester of pregnancy, 10% of women may develop clinically significant sleep apnea, particularly if obese (Pien et al 2005).

**Prevention**

Education pertaining to sleep, sleep hygiene, and awareness of sleep disorders is probably the most important means of prevention. The 10 Commandments of Sleep Hygiene are posted on the World Sleep Day® website. High school and college students learn little about sleep and the effects of sleep deprivation. Although physicians are well positioned to educate patients about sleep and sleep disturbance, they also receive little education on this topic. For example, the median total time devoted to teaching medical students in the United Kingdom about sleep and sleep disorders is 20 minutes (Stores and Crawford 1998).

Obesity and the metabolic syndrome may underlie the epidemic progression of sleep disordered breathing (Peppard et al 2000b). Bariatric surgery has become a popular form of treatment for morbidly obese patients.

Sudden death in sleep may be preventable. The quasi-epidemic of nocturnal sudden death affecting young men of Southeast Asian extraction may be due in part to the Brugada syndrome, a channelopathy that may lead to cardiac arrest. In patients suspected of harboring the Brugada syndrome, implantation of an automatic cardioverter-defibrillator could be lifesaving (Brugada et al 2003).

CPAP use delayed the age of onset of mild cognitive impairment (72.11 years vs. 82.10; p < 0.01) (Osorio et al 2015).

**Differential diagnosis**

The differential diagnosis for patients with sleep disorders depends on the signs and symptoms. The *International Classification of Sleep Disorders, 3rd Edition*, provides a comprehensive nosology of sleep disorders (American Academy of Sleep Medicine 2014).

Sleep disorders caused by medical, neurologic, and psychiatric disorders are not primary sleep disorders; they tend to vary in severity with the underlying disorder. For example, disturbed sleep is a prominent symptom in many patients with major depression and is common in a variety of medical diseases, including chronic obstructive pulmonary disease, end-stage renal disease, and congestive heart failure. Sleep disorders are prominent in various neurologic disorders (Culebras 2007b). Patients with Parkinson disease complain frequently about their sleep problems (Schapira 2000) and may exhibit REM sleep behavior disorder as early as 12 years before the onset of classic motor signs of extrapyramidal motor disorder. Patients with headache disorders commonly have sleep disruption, or the occurrence of their headache is modulated by the sleep pattern. Patients with multiple sclerosis may have an intrinsic form of hypersomnia as well as patients with myotonic dystrophy and other more rare neuromuscular conditions. Epilepsy and sleep are intimately linked, and some seizure variants appear exclusively during nocturnal sleep. Parasomnias need to be differentiated from other ictal events occurring at night including seizures. In many instances testing in the sleep laboratory is necessary.

The possibility that complaints of disturbed sleep or daytime sleepiness are not due to disordered sleep must also be considered. Patients with complaints of fatigue or tiredness may believe that their symptoms are due to abnormal sleep when in fact they are more often related to medical or psychiatric illness. A loss of a sense of well-being,
difficulty with attention and concentration, and an inability to function at an expected level may also be attributed erroneously to disturbed sleep. With each of these symptoms, a sleep disturbance may be the cause, but other diagnoses are more likely.

**Diagnostic workup**

For some patients, diagnosis can be established based on the history and the physical examination with no need for laboratory testing or additional evaluation. In other patients, the diagnosis may be strongly suspected, but laboratory tests are needed to determine the severity of the disorder and thereby direct treatment (Culebras 2004; Kushida et al 2005). For example, obstructive sleep apnea may be strongly suspected based on the history and physical examination, but treatment recommendations may depend on the frequency of apneas, the severity of associated hypoxemia and sleepiness, and the occurrence of cardiac arrhythmias. Sleep logs, in which the patient records the times and amounts of sleep obtained over 1 or more weeks, are helpful, particularly in patients with suspected circadian rhythm sleep disorders and in those with insomnia.

Complete blood count, serum chemistries, and thyroid function tests may be indicated in selected patients. Pulmonary function tests, including arterial blood gases, are helpful if alveolar hypoventilation syndrome due to obesity or neuromuscular disease is a consideration. Human leukocyte antigen testing may be useful in some cases of suspected narcolepsy. Urine toxicology screen may uncover evidence of drug abuse that is contributing to or causing sleep disturbance.

Polysomnography, with simultaneous monitoring of EEG, eye movements, heart rate, respiratory effort and airflow, oxygenation, and muscle tone, is used to confirm the diagnosis of sleep apnea and to assess the severity of associated sleep disruption and hypoxemia (George 1996; Bloch 1997). Polysomnogram is also useful in the diagnosis of narcolepsy and in some cases of suspected periodic limb movements, nocturnal epilepsy, REM sleep behavior disorder, and other parasomnias. Although polysomnography is not required for diagnosis in many patients with complaints of insomnia, it may be helpful in some patients with refractory insomnia or in whom sleep state misperception is suspected (Anonymous 1995). The multiple sleep latency test also provides diagnostically useful information and is performed the day after nocturnal polysomnography (Association of Sleep Disorders Centers Task Force 1986). With this test, patients are asked to nap for up to 20 minutes at 2-hour intervals; the time to the onset of sleep (sleep latency) and from sleep onset to the onset REM sleep (REM-sleep latency) are calculated for each nap. The mean sleep latency provides a measure of the severity of sleepiness, and the occurrence of REM sleep in 2 or more naps is diagnostic of narcolepsy. The Maintenance of Wakefulness Test (MWT) is designed to test the capacity of the individual to remain awake over 40 minutes of testing time in the sleep laboratory (Littner et al 2005).

Portable monitoring devices that record esophageal acidity, electrocardiogram, movements, or sleep-wake electroencephalogram may be useful in selected patients (Broughton et al 1996). For example, wrist actigraphy, a device that monitors body movements over an interval of hours to weeks, may provide a cost-effective approach to diagnosis of some patients with insomnia or circadian disturbances (Littner et al 2003).

Although laboratory polysomnography is the preferred diagnostic modality, portable monitoring has been developed as an alternative diagnostic approach for sleep apnea evaluation. A portable monitor records fewer physiologic variables but is typically unattended and can be performed in the home. In March 2008, the U.S. Centers for Medicare and Medicaid Services released a statement allowing the use of portable monitoring to diagnose sleep apnea and to prescribe continuous positive airway pressure. This action has opened the door for more widespread use of unattended portable home monitoring devices (Collop 2008).

Cerebral function can be studied with neuroimaging techniques in sleep in human subjects. Work has provided provocative images of the dormant brain (Dang-Vu et al 2007). Human brain activity during sleep alternates within specific areas in relation to the sleep stage and previous waking activity. The work on neuroimaging has provided new data that describe some aspects of the pathophysiology of disorders such as insomnia, sleep apnea, and restless legs syndrome. Future studies, conducted with state of the art techniques on large numbers of patients, will be able to
address important issues related to sleep and contribute significantly to the understanding of the neural basis of sleep pathophysiology. This will offer the opportunity to use neuroimaging in correlation with clinical and electrophysiological evaluations as a helpful tool in the diagnosis, classification, treatment, and monitoring of sleep disorders in humans.

Measurement of hypocretin-1 in CSF may play a role in the diagnosis of narcolepsy. The test results should be interpreted within the clinical context. Mignot has determined that 110 pg/ml of hypocretin-1 in CSF is the cut-off value to diagnose narcolepsy (Mignot et al 2002). Patients with idiopathic hypersomnia, sleep apnea, restless legs syndrome, or insomnia have normal hypocretin-1 levels. Patients with narcolepsy-cataplexy have predicted values of less than 110 pg/ml with a specificity of 99% and a sensitivity of 87%, which is higher than for the multiple sleep latency test. When cataplexy is absent or atypical, the predictive power is limited with high specificity (99%) but low sensitivity (16%). Most of these patients will have normal hypocretin-1 values, creating a dilemma for the clinician because this is precisely the group of patients in need of accurate diagnostic studies. The measurement of hypocretin-1 in CSF may be most useful in cases of narcolepsy without cataplexy, in children with excessive somnolence who have not, as yet, developed cataplexy, when the multiple sleep latency test is difficult to interpret because of medication effect, or in psychiatric conditions (Mignot et al 2002; Mignot 2005).

**Management**

Management depends on the particular sleep disorder. A decision memorandum posted by The Centers for Medicare and Medicaid Services on October 30, 2001, reviews the guidelines for authorized use of CPAP for the treatment of obstructive sleep apnea (Health Care Financing Administration 2001). Under these guidelines, CPAP will be covered under Medicare in adult patients with obstructive sleep apnea if either of the following criteria is met: apnea-hypopnea index greater than 15, or apnea-hypopnea index greater than 5 and less than 14 with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.

AutoPAP devices adapt to the required nocturnal airway pressures from breath to breath and record compliance with the machine over many weeks of treatment.

A novel treatment for obstructive sleep apnea consists of adapting an oral interface connected to a pump that creates a negative pressure within the oral cavity while the subject sleeps (Colrain et al 2013). The objective is to create a pressure gradient that draws the soft palate anteriorly towards the tongue to permit improved oropharyngeal airflow during sleep. In a multicenter study of 63 subjects, the average nightly usage was 6.0±1.4h. There were no severe or serious adverse events, and the authors concluded that clinically significant improvements in sleep quality and continuity were achieved with this device. The FDA has approved a neurostimulator implant for sleep apnea as a second-line therapy (Strollo et al 2014). The implant keeps the airway open by stimulating the hypoglossal nerve during inspiration in sleep. Contraction of upper airway muscles causes the base of the tongue to move forward. The device pre-empts getting an MRI scan.

**Sodium oxybate** (gamma hydroxybutyrate, GHB) is the drug of choice for treating patients with narcolepsy who experience episodes of cataplexy (Anonymous 2002) not responding to traditional stimulants of wakefulness. Because of safety concerns associated with the use of the drug (known popularly as the date-rape drug), the distribution of sodium oxybate is tightly restricted to registered physicians and only dispensed out of 1 central pharmacy in the entire United States.

Treatment for chronic insomnia includes cognitive behavioral therapy (CBT) and pharmacologic treatments, both of which are complementary (Winkelman 2015). Cognitive behavioral therapy targets dysfunctional behaviors and beliefs that perpetuate insomnia. Cognitive behavioral therapy is conventionally delivered in 6 to 8 settings by therapists with training in sleep disorders. The efficacy of cognitive behavioral therapy depends on adherence to rules that require discipline and regimentation like sleep restriction, reduced arousals in sleep environment, and sleep hygiene. Pharmacologic therapy includes administration of benzodiazepine receptor agonists (temazepam, lorazepam, eszopiclone, zolpidem, zaleplon, triazolam), antidepressants with sedating effect (trazodone, doxepin, mirtazapine), and anticonvulsants (gabapentin).

Hypnotic drug development has been focused on the orexin (hypocretin) system that promotes wakefulness. Suvorexant (Merck, MK-4305) is the first compound of the dual orexin receptor antagonist (DORA) class approved by the FDA (Sullivan 2012). This agent has a more focal target on a specific receptor than the GABA agonists that target a
widespread array of receptors and, therefore, has less potential for adverse effects. Suvorexant does not depress the respiratory function or the central nervous system and may be safe for patients with sleep apnea.

The FDA has approved a device for restless legs syndrome sufferers that consists in a pad that provides vibratory counterstimulation to the legs that gradually ramps down and shuts off at the onset of sleep. The device is a noninvasive, nonpharmacologic alternative for patients with restless legs syndrome and difficulty initiating sleep. More information on this device can be found on the Sensory Medical, Inc.

Melatonin administration continues to puzzle clinicians. Melatonin is a hormone secreted by the pineal gland with widespread effects in circadian-related systems. Despite its potent action, melatonin is sold in the United States without prescription and is considered by most to be a hypnotic, which it is not. Clinical observations indicate that melatonin may improve and even affect the natural history of REM sleep behavior disorder, perhaps by changing the behavior of REM sleep in subjects who take it (Kunz 2013). Clinical trials are being considered to test the efficacy and safety of melatonin. A melatonin agonist (ramelteon) has shown small benefits for time to sleep onset.

Special considerations

**Pregnancy**

Pregnancy may be associated with altered breathing during sleep. In the third trimester of pregnancy, reduced functional respiratory residual capacity due to weight gain and changes in the shape of the diaphragm and thorax can alter respiratory function and increase the incidence and severity of sleep-disordered breathing. Up to 10% of pregnant women are at risk for development of sleep apnea (Pien et al 2005). The condition may lead to arterial hypertension and endothelial dysfunction.

Preeclamptic toxemia is characterized by hypertension, proteinuria, and edema. Preeclampsia may affect 7% to 10% of all pregnancies in the United States (Granger et al 2002) and constitutes a major cause of fetal and maternal morbidity and mortality. The likely triggering event in preeclampsia is placental ischemia (Gilbert 2008), which may precipitate the release of a cascade of active factors from the placenta that generate profound effects on the maternal cardiovascular system causing hypertension and endothelial dysfunction.

Sleep apnea in pregnancy may cause placental hypoxia. It has been proposed that at the very least, sleep apnea is a significant contributing factor for the development of preeclampsia, in particular in pregnant women who are vulnerable for the occurrence of sleep apnea (Yinon et al 2006; Perez-Chada et al 2007). Overweight women and women with metabolic syndrome are at particular high risk for development of sleep apnea and in consequence preeclampsia.

Overnight ambulatory unattended polysomnography is a reasonable test to use in the third trimester of pregnancy at home in women who snore, report sleepiness, and show hypertension. The aim would be to objectively demonstrate and measure clinically significant sleep apnea. A sleep apnea-hypopnea index of 5 per hour of sleep or more might lead to the indication of continuous positive airway pressure treatment.

In a prospective study of 12 pregnant women, Guilleminault and associates concluded that early application of nasal CPAP in pregnant women alleviated sleep-related breathing disturbances but was not sufficient to prevent negative pregnancy outcomes (Guilleminault et al 2007). Obesity and prior preeclampsia appeared to be important risk factors and were associated with the worst complications. In a parallel study, Poyares and colleagues indicated that in pregnant women with hypertension and chronic snoring, nasal CPAP use during the first 8 weeks of pregnancy combined with standard prenatal care was associated with better blood pressure control and improved pregnancy outcomes (Poyares et al 2007).

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**References especially recommended by the author or editor for general reading.

**Former authors**

Michael Aldrich MD (original author)

**ICD and OMIM codes**

**ICD codes**

ICD-9:
- Disorder, sleep: 780.50
- Disorder, sleep, initiation or maintenance: 780.52
- Disorder, sleep, nonorganic origin (transient): 307.41
- Disorder, sleep, persistent: 307.42
- Disorder, sleep, specified type NEC: 307.49
- Disorder, sleep, specified NEC: 780.59

ICD-10:
- Sleep disorder, unspecified: G47.9
- Disorders of initiating and maintaining sleep [insomnias]: G47.0
- Nonorganic insomnia: F51.0
- Other nonorganic sleep disorders: F51.8
- Other sleep disorders: G47.8

**Profile**

**Age range of presentation**

- 0-01 month
- 01-23 months
- 02-05 years
- 06-12 years
- 13-18 years
- 19-44 years
- 45-64 years
- 65+ years

**Sex preponderance**

male=female

**Family history**

none

**Heredity**
Population groups selectively affected

Occupation groups selectively affected

Differential diagnosis list

sleep disorders caused by medical disorders
sleep disorders caused by neurologic disorders
sleep disorders caused by psychiatric disorders
major depression
chronic obstructive pulmonary disease
end-stage renal disease
congestive heart failure
Parkinson disease
headache disorders
multiple sclerosis
myotonic dystrophy
other more rare neuromuscular conditions
epilepsy
medical or psychiatric illness
loss of a sense of well-being
difficulty with attention and concentration
inability to function at an expected level

Other topics to consider

Circadian rhythm sleep disorder: free-running type
Drug-induced sleep disorders
Irregular sleep-wake rhythm disorder
Obstructive sleep apnea
Parasomnia overlap disorder and status dissociates
Rapid eye movement sleep behavior disorder
Sleep bruxism
Sleep and anxiety disorders
Sleep and depression
Sleep and epilepsy
Sleep and headaches
Sleep and medical disorders
Sleep and mental disorders
Sleep and multiple sclerosis
Sleep terror

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