# Sleep Disorders

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- Complete the questions at the end of the course.
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### *Faculty Disclosure*

Contributing faculty, Teisha Phillips, RN, BSN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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***Course Objective***

Many of the complications associated with sleep disorders are preventable, making early diagnosis and appropriate treatment vital. The purpose of this course is to provide healthcare professionals with the information necessary to identify and effectively treat sleep disorders, thereby improving patients' quality of life and preventing possible complications.

***Learning Objectives***

*Upon completion of this course, you should be able to:*

1. Discuss the physiology of normal sleep.
2. Describe the classification of sleep disorders.
3. Compare and contrast the types of insomnias and their associated diagnosis and treatment.
4. Evaluate the major types of sleep-related breathing disorders, particularly obstructive sleep apnea.
5. Identify the clinical signs and symptoms of narcolepsy.
6. Outline the characteristics of non-narcolepsy hypersomnias.
7. Analyze the complications and symptoms of circadian rhythm sleep disorders.
8. Describe the characteristics, diagnosis, and treatment of parasomnias.
9. Evaluate the presentation and treatment of sleep-related movement disorders.
10. Assess considerations for patients with sleep disorder who have low English literacy.

***Pharmacy Technician Learning Objectives***

*Upon completion of this course, you should be able to:*

1. Describe normal and disordered sleep.
2. Compare and contrast the various types of sleep disorders.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

## INTRODUCTION

Sleep is one of the most vital processes of life and serves many important functions, including preservation, restoration, and memory processing. Repeated disruption of the natural sleep cycle or failure to initiate sleep (i.e., sleep disorder) can lead to a sleep deficit, which in turn causes physical, mental, and emotional fatigue. Most individuals with a sleep disorder experience a myriad of symptoms and a reduction in quality of life [1].

The American Academy of Sleep Medicine (AASM) publication *The International Classification of Sleep Disorders, Third Edition, Text Revision* (ICSD-3-TR) identifies more than 80 official sleep disorders [2]. Many are uncommon, but a handful (e.g., insomnias, obstructive sleep apnea, narcolepsy, restless legs syndrome) affect millions of Americans and are responsible for significant morbidity and mortality, including direct physiologic and/or psychological complications and accidents associated with moderate or severe drowsiness.

It is estimated that 50 to 70 million adult Americans have a sleep or wakefulness disorder [1]. Some of the most serious long-term health consequences of sleep disorders (or sleep insufficiency/deficit) include glucose intolerance, increased blood pressure, increased inflammatory markers, higher evening cortisol levels, weight gain/obesity, and an increased risk of myocardial infarction, depression, and cancer [1; 3; 4]. Additionally, the National Highway Traffic Safety Administration (NHTSA) estimates that in 2017, 91,000 police-reported crashes involved drowsy drivers. These crashes led to an estimated 50,000 people injured and nearly 800 deaths. In 2022, there were 693 deaths from drowsy-driving-related crashes [5].

The economic cost of sleep disorders should not be underestimated. One study found that individual healthcare costs were approximately doubled for patients with undiagnosed obstructive sleep apnea [6]. Research commissioned by Congress in 1993 found that direct annual medical costs for insomnia were $15.2 billion (with the amount spent on over-

the-counter products not included), and that the indirect and related annual costs (mostly costs arising from accidents) approached $56 billion [4; 7; 8; 9]. In 2020, the aggregate total of direct and indirect insomnia healthcare costs has been estimated to be as high as $100 billion U.S. dollars per year [10]

Sleep deprivation leads to daytime sleepiness, fatigue, inattentiveness, and prolonged reaction time, all having a negative impact on performance, productivity, and safety in the workplace. A 2011 study found that annual workplace losses (including workplace accidents) due to insomnia and associated comorbidities totaled $91.7 billion per year [11]. The study, using extrapolated data from 7,428 U.S. workers enrolled in healthcare plans, found that presenteeism (i.e., attending work while drowsy) accounted for the majority of the losses (roughly two-thirds) and absenteeism accounted for the remainder. Comorbidity is a major factor, yet after 26 conditions were controlled for, the net annual cost of lost productivity resulting from insomnia alone was $63.2 billion [11]. One limitation of the study was that only data from workers with healthcare insurance were sampled. Although the prevalence of insomnia may be similar among insured and uninsured populations, undiagnosed and untreated sleep disorders can amount to greater overall long-term cost. A 2015 study reiterated the negative impact on work performance (e.g., absenteeism, presenteeism, workplace injury, accidents driving to/from work) of one sleep disorder in particular, obstructive sleep apnea [12].

Sleep disorders have a clear impact on productivity and public health. The AASM and the Institute of Medicine emphasize that education on somnology and sleep medicine should be incorporated into continuing education programs [1]. Many of the complications associated with sleep disorders are preventable, making early diagnosis and appropriate treatment vital. Unfortunately, research indicates that sleep disorders continue to be underdiagnosed and undertreated [13; 14; 15; 16]. One study of relatively healthy patients seeking preventive care found that 57% either reported a sleep complaint related to sleep apnea or were found to be at increased risk for the condition [14]. However, only 11% of individuals who reported sleep complaints underwent any subsequent diagnostic testing, indicating a gap in factual knowledge and appropriate clinical behaviors [14]. Infectious disease outbreaks, such as the 2019 novel coronavirus (2019-nCoV/SARS-CoV-2 [COVID-19]) pandemic, increase the prevalence of psychological distress and impose symptoms that adversely affect sleep quality [17; 18]. A systematic review and meta-analysis, conducted to examine the impact of the pandemic on the prevalence of sleep problems among the general population, healthcare workers, or patients with COVID-19, found a prevalence of approximately 40% among the general and healthcare populations, with a higher prevalence of sleep problems among patients with active COVID-19 [19]. The review included a total of 44 studies published after March 2020 that involved 54,231 participants from 13 countries.

This course will provide information regarding the physiology of sleep; the causes, risk factors, epidemiology, and pathophysiology of various sleep disorders; diagnosis, including patient history, assessment of sleep habits, physical examination, laboratory tests, and sleep studies; and treatments to improve sleep patterns, including lifestyle/behavioral change (e.g., "sleep hygiene"), pharmacologic interventions, surgical interventions, and other treatment options for patients.

## THE PHYSIOLOGY OF SLEEP

The sleep-wake cycle occurs naturally in humans as well as all animal species, an indication that sleep serves some vital function. Sleep is marked by suspended consciousness, diminished sensory activity, relaxed musculature, reduced ability to react to stimuli, and other changes in brain activity that correspond with distinct sleep phases. Common experience demonstrates that sleep is restorative and that sleep deprivation impairs brain function. Despite being necessary to humans, the basis for the need of sleep is still poorly understood, as are the long-term effects of disruption in the sleep-wake cycle. To date, the observed behavioral consequences of acute sleep deficit have provided the clearest indication of those functions served by natural sleep.

Studies conducted over the past two decades suggest that sleep is critical for maintaining metabolic homeostasis within the human brain [144; 145]. Metabolic byproducts, including amyloid-beta and tau proteins linked to neurodegenerative diseases, accumulate in the interstitial fluid compartment surrounding brain cells. Interstitial fluid waste products of peripheral organ metabolism diffuse into lymphatic channels that drain into the venous circulatory system and thence transported to the liver for degradation. There is no conventional lymphatic system in the brain; elimination of potentially toxic proteins and other metabolites is dependent on a system of recirculating cerebrospinal fluid (CSF) and interchange with interstitial fluid, organized around the microvasculature, with interstitial fluid proteins and other byproducts exiting along the venules. This convective pathway is named the glymphatic system in recognition of its dependence on astrocytic aquaporin-4 water channels, and the functional similarity to peripheral lymphatic removal of interstitial metabolic byproducts.

The interstitial concentration of metabolic waste products is higher during periods of wakefulness and lower during sleep, suggesting that glymphatic clearance is increased during sleep and regulated by the sleep-wake cycle [144]. Using an experimental animal model, researchers have shown that sleep is associated with a 60% increase in brain interstitial space volume, acceleration in glymphatic system fluxes, and increased rates of amyloid-beta and tau clearance [144]. Chronic sleep deprivation was associated with an increase in tau accumulation and spread of tau pathology within brain tissue [145]. Thus, the restorative function of sleep may be linked with enhanced removal of potentially toxic waste products that accumulate in the awake central nervous system.

## CIRCADIAN RHYTHMS, HOMEOSTASIS, AND THE SLEEP-WAKE CYCLE

The sleep-wake cycle consists of approximately 8 hours of sleep and 16 hours of wakefulness in healthy adults and is controlled by two internal factors: circadian rhythms and sleep homeostasis [20]. Circadian rhythms are "physical, mental, and behavioral changes that follow a roughly 24-hour cycle, responding primarily to light and darkness in an organism's environment" [21]. Biologic "clocks" located throughout the body manage circadian rhythms in individual body systems; these are all controlled and coordinated by the suprachiasmatic nucleus (SCN), or "master clock," located in the hypothalamus. The SCN's circadian rhythm has an endogenous component but is also driven by external cues from the environment, called zeitgebers [22]. The light-dark cycle is the overwhelmingly dominant zeitgeber for humans. Light acts on photosensitive ganglion cells in the retina that send signals directly to the SCN, providing synchronization with the particular environment. Thus, the body is able to adapt (in some cases with difficulty) and correct the sleep-wake cycle relative to differing light-dark conditions (e.g., when travelling to a different time zone).

Endogenous circadian rhythms, and therefore sleep needs, vary among individuals and age groups. Adolescents typically need 9.5 hours of sleep, and infants require 16 hours of sleep [23]. There are three chronotypes (identifiable using the Horne-Östberg questionnaire): morning type, an early circadian phase; evening type, a late circadian phase; and intermediate type. This is important because morning-type individuals typically sleep earlier and longer and are quicker to adjust to changes in sleep schedules than intermediate and evening types [23; 24]. One study found that morning-type individuals are also less likely to deviate from their normal sleep schedule regardless of social cues (e.g., being on vacation) [23]. One study found that adolescents living in brightly lit, urban environs had a "stronger evening-type orientation than adolescents living in darker and more rural municipalities" [25]. The study also found that nighttime electronic-screen media use (i.e., a strong artificial light source) correlated with an evening-type rhythm in adolescents

living in darker areas, but a morning rhythm could be established if limited and appropriate nighttime lighting (e.g., dimmer room lights, heavy curtains to block street lighting, no electronic-screen media use) was used.

Although the primary zeitgeber in humans is the light-dark cycle, there are other influential nonphotic cues, including exercise, temperature, and various social cues, that influence the regulation of various biologic processes (e.g., body temperature, hormone production) [23; 26; 27]. Researchers propose that sleep patterns may be influenced by other important zeitgebers, including sound, temperature, and the earth's magnetic field, that are as yet unproven or only considered weak factors [28; 29]. Given that light is such a powerful influence and that humans are sensitive to very low levels of light, it is difficult to study the effects of these other possible cues. (Blind individuals typically have "free running" circadian rhythms ≥25 hours and are often the subject of zeitgeber investigations.) Some zeitgebers, such as aberrant work schedules, alarm clocks, artificial light, radio, television, and time-zone change, are known to cause disruptions to the natural sleep-wake cycle.

Homeostasis is the body process associated with maintaining a steady state of internal conditions (e.g., acid-base balance, blood pressure, body temperature). The sleep drive and amount of sleep are also under homeostatic control [30]. The neurochemistry of sleep is not fully understood, but the neurotransmitter adenosine is thought to have an important role as a homeostatic regulator of sleep [30; 31]. Adenosine does not act as a classical neurotransmitter; it is neither stored nor released, but is instead thought to be formed inside or on the surface of cells [30; 31]. The drive for sleep (and, alternately, wakefulness) has been found to be directly related to extracellular adenosine levels in the cerebral cortex and basal forebrain [31]. Concentrations of the chemical increase throughout the day and decrease during the sleep recovery period, and the feeling of intense sleepiness following prolonged wakefulness is thought to be caused by very high adenosine levels. Adenosine is a theoretical link between the humoral and neural mechanisms of sleep-wake regulation [31].

Produced in the pineal gland, melatonin is another key sleep hormone. It is regulated by darkness signals from the SCN and also provides feedback to that circadian oscillator [32; 33]. Circulating melatonin levels increase in the hours following nightfall and drop significantly upon eye exposure to light. It is believed that this hormone supplements and reinforces the entraining effects of the light period [32]. Whereas the ganglion cells provide a light cue to the SCN, melatonin provides a darkness cue via receptors in and around the structure [33].

## SLEEP STAGES

The sleep process consists of four stages of sleep, divided into two general categories: rapid eye movement (REM) sleep and non-REM sleep (NREM). These stages are divided into five phases: wake, N1, N2, N3, and R [34]. While both alpha and beta waves are present during open-eye wakefulness, beta predominates. As drowsiness increases and the eyes close, the alpha rhythm becomes predominant [34].

NREM sleep consists of three distinct stages (N1, N2, N3), each of which is defined by a set of unique electrophysiologic parameters, including electroencephalogram (EEG), electromyogram (EMG), eye movements, and respiration [34]. When awake, EEG measurements of brainwave activity show frequencies of 8 Hz or greater. When a patient is awake but relaxed with eyes closed, EEG measurements fall in the alpha range (8 to 12 Hz) when measured at posterior head regions. In children, this basic rhythm is in the theta range (4 to 8 Hz), and in infants, it is in the delta range (slower than 4 Hz). A return to wakeful levels of brain activity (greater than 12 Hz) occurs if the subject opens his or her eyes or engages in mental activity. When awake or when relaxing with eyes closed, muscle tone is normal and individuals are fully aware of their surroundings.

### N1 (Stage 1)

During stage 1 sleep, individuals begin to feel drowsy but can be easily aroused. Relaxation of musculature begins, as does reduced environmental awareness [20]. Slow and rolling lateral eye movements also may occur. EEG brain activity shows interruption of the posterior dominant rhythm (i.e., alpha dropout)

and the onset of a low-voltage, intermixed pattern of frequencies [35; 36]. Positive occipital sharp transients of sleep (POSTS) and very brief vertex sharp waves may occur in repetitive runs. (POSTS start around 4 years of age, are common by 15 years of age, and decline after 50 years of age.) Hypnagogic hypersynchrony, or bursts of high-amplitude, diffuse, rhythmic (sinusoidal) delta activity, can arise, especially among children 3 months to 13 years of age and is considered a normal variant of drowsiness in this age group. This stage tends to last one to five minutes, consisting of around 5% of the total cycle [34].

**N2 (Stage 2)**

Approximately 50% of time is spent in stage 2 sleep during an adult's normal night's sleep [20; 34]. Arousal is more difficult during this phase, and the low-voltage, intermixed pattern continues. Brainwave activity slows to the theta range (4 Hz to 7 Hz). Sleep spindles (and associated K-complexes) are the defining characteristic of stage 2 sleep. Spindles are short bursts of vertex rhythmic activity between 12 and 16 Hz (typically 14 Hz) lasting about 0.5 seconds. Sleep spindles begin at 6 to 8 weeks of age and continue throughout life [34; 35; 36].

**N3 (Stage 3)**

This is considered the deepest stage of sleep [34]. Muscle tone continues to decrease progressively through stage 3. Arousal is most difficult during these stages, which are marked by slow-wave sleep consisting of progressively increasing high-voltage, delta-range brain activity. During stage 3, delta activity comprises as much as 50% or more of brainwave activity [35; 36]. Sleep spindles may still occur in these stages but are not a major feature. Over a lifetime, the amount of time spent in slow-wave sleep decreases [20]. Cognitive testing shows that individuals awakened during this stage tend to have mental performance that is moderately impaired for 30 minutes to 1 hour [34]. During N3, the body repairs and regrows tissues, builds bone and muscle, and strengthens the immune system [34].

**REM Sleep**

As the name suggests, the major feature of REM sleep is rapid eye movement, but this stage is also characterized by muscle atonia and EEG desynchronization [20]. Brainwave activity returns to a low-voltage intermixed pattern and becomes faster (beta and theta range), almost resembling wakefulness. Dreaming is most likely to occur in this stage. Central activity in the theta range can produce waves with a "saw tooth" appearance on a polysomnogram display.

In healthy adults, about four or five sleep cycles, each about 90 minutes, occur in one night, each one progressing through the non-REM stages, followed by REM sleep [20]. Slow-wave sleep is lessened and REM sleep becomes more predominant with each successive sleep cycle [37].

Some individuals enter REM sleep before descending through non-REM phases, which is referred to as sleep-onset REM periods (SOREMPs). This is considered an indicator of a sleep disorder, usually narcolepsy, but it may also occur in patients with obstructive sleep apnea [33; 38]. SOREMPs are uncommon in the healthy adult population but are slightly more prevalent in individuals with excessive sleepiness (e.g., adolescents and young adults, shift workers) [39]. SOREMPs are also seen with other disorders, including Prader-Willi syndrome, Kleine-Levin syndrome, Parkinson disease, and periodic limb movement disorder (PLMD) [40].

## AGING, THE SLEEP CYCLE, AND DEMENTIA

As noted, sleep promotes glymphatic clearance of metabolic waste from the brain, and this function is optimized in the deepest non-REM sleep stage, N3 or slow-wave sleep [144]. Disruptions in sleep-stage architecture and continuity occur with aging. These changes include increase in time required to fall asleep, shortened nocturnal sleep duration, increase in the number and duration of nocturnal awakenings, more frequent daytime naps, and decreased slow wave sleep. The circadian system and sleep

homeostatic mechanisms (e.g., glymphatic clearance) also become less robust with normal aging [146]. The degree and prevalence of sleeplessness among older adults increases with aging, as does the potential adverse effects associated with sleep deprivation.

Mounting evidence from animal model and clinical observational studies implicates persistent sleep disruption as a risk factor for future Alzheimer disease (AD) and other forms of dementia. Chronic sleep deprivation promotes accumulation of amyloid-beta and tau proteins in brain tissue, aggregates of which are the defining pathologic features of AD. The relationship is complex and possibly bi-directional—chronic sleep disorder is a common byproduct of AD in aging adults and/or a risk factor (mechanism) for augmenting the progression of pathologic features that lead to AD with aging. A systematic review and meta-analysis found that individuals with sleep problems had a higher risk of cognitive impairment, preclinical AD, and frank AD than did those without sleep problems, respectively [147].

Using data from a subset of Framingham Heart Study participants who had completed two overnight sleep studies (polysomnography) within a three-year period and were then available for an extended follow-up, investigators sought to determine whether slow-wave sleep loss with aging is associated with risk of incident dementia. The cohort comprised 346 participants 60 to 87 years of age (mean age: 69 years). In this study, the percentage of time in slow-wave sleep decreased each year, accelerating from 60 years of age onward before peaking at 75 to 80 years of age. Fifty-two cases of dementia were observed over a mean follow-up of 12 years. Analysis showed that each percentage decrease in deep sleep was associated with a 27% increase in risk for all-cause dementia and 32% increase in risk for AD [148]. These data demonstrate that the proportion of time spent in N3 slow-wave sleep declines over time in aging adults (thereby reducing the optimal period for glymphatic clearance) and that greater declines are associated with the risk of future dementia [148].

## OVERVIEW OF SLEEP DISORDERS

As discussed, there are more than 80 official sleep disorders defined in the current AASM diagnostic and coding manual, the ICSD-3-TR [2]. The ICSD-3-TR uses a pragmatic framework for categorizing sleep disorders based primarily on pathophysiology, if known, and also phenomenology and organ system methodology [2]. Unlike in original versions, disorders are no longer grouped into three major classes: dyssomnias, parasomnias, and sleep disturbances associated with mental, neurologic, or other medical disorders. Instead, the ICSD-3-TR contains seven major categories of sleep disorders [2]:

- Insomnia
- Sleep-related breathing disorders
- Central disorders of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep-related movement disorders
- Other sleep disorders

A goal of the ICSD-3-TR framework was to organize sleep disorders into an International Classification of Diseases (ICD-10)-compatible format [2]. Another goal was to describe in detail all currently recognized sleep and arousal disorders, which is a missing feature of other manuals, including the widely used *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR), while still maintaining a good degree of concordance with the DSM-5-TR.

## DSM-5-TR CLASSIFICATION

The DSM-5-TR contains information for making a diagnosis of a sleep disorder; however, it has less detailed descriptions of certain sleep-wake disorders than the ICSD-3-TR. For example, the DSM-5-TR section on insomnia disorders does not extensively describe each of the three forms of insomnia described in the ICSD-3-TR. The DSM-5-TR takes what it refers to as a "lumping versus splitting" approach to classifying sleep-wake disorders. The insomnias identified in the ICSD-3-TR fall under the general category of insomnia disorder in the DSM-5-TR, lumped together due to their similar presentations and impact on clinical care for non-specialists. Insomnia disorder is defined by the DSM-5-TR as difficulty initiating sleep, difficulty maintaining sleep, or experiencing early morning awakenings. Symptoms must be present for at least three months, occur at least three nights per week, cause significant distress or impairment, and cannot be explained by coexisting medical or psychiatric disorders [136]. While this course incorporates information from both the DSM-5-TR and the ICSD-3-TR, the organization structure of the latter will be used as an outline. The following sections will discuss the more common examples of each of the seven categories, and those with the greatest incidence will be discussed in more detail.

## SLEEP STUDY TESTS

Many tests are available to assess the quality of an individual's sleep, and a discussion of each is beyond the scope of this course. However, the most commonly used tests are polysomnography and the multiple sleep latency test (MSLT), both of which are used in the evaluation of many sleep disorders.

Polysomnography is preferably conducted by a certified sleep technologist at an AASM-accredited facility. This test monitors many physiologic parameters, including electrocardiogram, EEG, eye movements (electrooculogram), chin EMG, airflow, oxygen saturation, respiratory effort, and heart rate [41]. A technician will note if snoring is present and, if so, the degree (i.e., mild, moderate, or severe). Body position and leg EMG derivations are also recommended.

One full-night study is typical, but split-night studies (i.e., polysomnography followed by continuous positive airway pressure [CPAP] titration) may be used when initial monitoring shows a high apnea-hypopnea index (AHI) score. This index will be discussed in detail later in this course. The *AASM Manual for the Scoring of Sleep and Associated Events* is used to set up and analyze the study, and the results are reported as an AHI score (or a respiratory disturbance index) for review by a qualified sleep physician. Polysomnography can help rule out the possibility of sleep disorders, and it will also show if the patient's sleep cycle is normal or if REM sleep occurs at unusual times.

Portable monitor testing has a known likelihood of producing false-negative results; therefore, it is considered inferior to overnight sleep lab polysomnography [41]. Airflow, blood oxygenation, and respiratory effort are the minimum test parameters needed for a complete at-home study. The sensors are similar or identical to those used for polysomnography and will either be placed by a sleep technologist, other trained professional, or the patient following detailed instruction. The AHI score is calculated per the *AASM Manual* using the truncated portable monitor test data. Tests of patients who have a high probability of obstructive sleep apnea and a low AHI should be considered inaccurate and should be repeated (in a sleep lab whenever possible) [41].

The MSLT is a daytime test that can determine if REM sleep patterns occur during wakefulness and monitor the amount of time it takes for the patient to fall asleep normally during the day. For example, sleep latency periods (i.e., the time it takes to fall asleep) are typically 8 minutes or less in narcoleptic patients, but healthy individuals usually take 12 or more minutes to fall asleep during the daytime [42].

## INSOMNIAS

The term insomnia is defined generally as difficulty with initiation, duration, consolidation, or quality of sleep. It is commonly applied when three conditions are satisfied: ample time and opportunity for sleep, persistent sleep difficulty, and daytime dysfunction associated with sleep deficit [2].

Chronic or short-term insomnia is a problem for most people at some point in their lives. Patients will experience problems going to sleep or staying asleep and are distressed by the number of hours they are awake at night or by a quality of sleep perceived as poor [2]. However, if daytime function is unaffected, the complaint does not warrant treatment other than discussion and education, because by definition they do not have an insomnia disorder. Patients with clinically significant insomnia typically become fatigued, irritable, cognitively impaired, and/or depressed and some complain of headaches, muscle tension, palpitations, work impairment, and social withdrawal [2].

There are now three formal insomnia diagnoses listed in the ICSD-3-TR: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder [2]. This is a significant departure from the previous version of the ICSD, which included 11 diagnoses. Many sleep disorders diagnosed in the past have a complaint of insomnia in common. These included adjustment insomnia (acute insomnia); psychophysiologic insomnia; paradoxical insomnia; idiopathic insomnia; insomnia due to mental disorder; inadequate sleep hygiene; behavioral insomnia of childhood; insomnia due to drug or substance; insomnia due to medical condition; insomnia not due to a substance or known physiologic condition, unspecified (nonorganic insomnia, not otherwise specified [NOS]); physiologic (organic) insomnia, unspecified (organic insomnia, NOS).

Insomnia is no longer regarded as either being due only to a primary sleep disorder or because of an underlying medical or psychiatric condition (i.e., as a primary disorder or as a disorder secondary to another comorbid condition). For one, the symptoms and features of primary and secondary insomnia overlap considerably, and differentiation was often difficult or impossible. Additionally, patients usually met the criteria for more than one ICSD-2 insomnia subtype. Evidence has shown that when a patient's underlying medical condition causing insomnia is treated, the insomnia often persists, or when the insomnia was treated, both the comorbid medical condition and the sleep disorder improved [2]. The first two categories of insomnia—chronic insomnia disorder and short-term insomnia disorder—now reflect an all-encompassing view of disordered sleep and are based on various levels of sleep dysfunction. The third category—other insomnia—is included in the ICSD-3-TR to describe individuals with difficulty initiating and maintaining sleep, but who do not meet the criteria for the other two categories. The AASM does not foresee many individuals receiving this diagnosis, and it will not be discussed in this course.

### CHRONIC INSOMNIA DISORDER

According to the ICSD-3-TR, chronic insomnia disorder is defined as "chronic sleep onset and/or sleep maintenance complaints with associated daytime impairment and is reserved for individuals whose sleep difficulties exceed minimal frequency and duration thresholds shown to be associated with clinically significant morbidity outcomes" [2]. This diagnosis encompasses many insomnia subtypes found in other texts, including primary insomnia, comorbid insomnia, chronic insomnia, secondary insomnia, sleep-onset association disorder, behavioral insomnia of childhood, disorder of initiating and maintaining sleep, and limit-setting sleep disorder. As discussed, this consolidation is not for the sake of simplicity, but reflects the actual state of current knowledge and evidence regarding chronic insomnia. The specific primary insomnia clinical/pathologic subtypes that are now considered part of this larger, global class in the ICSD-3-TR are shown in ***Table 1*** [2].

| CLINICAL AND PATHOPHYSIOLOGIC SUBTYPES IN THE ICSD-3-TR | | |
|---|---|---|
| **Diagnosis** | **Features** | **Symptoms** |
| Psychophysiologic insomnia | Elevated levels of somatic and cognitive arousal, especially when trying to sleep<br>Learned sleep-preventing associations<br>Excessive focus on sleep<br>Excessive worry about sleep | Difficulty sleeping in usual sleep setting (e.g., at home), but may fall asleep easily away from home or at home when not trying to sleep |
| Idiopathic insomnia | Early onset (i.e., infancy)<br>Genetic or congenital alterations in sleep-induction/arousal systems in the brain<br>No genetic markers are known | Gradual inability to sleep beginning at a very young age with no discernible cause |
| Paradoxical insomnia | Individuals underestimate the amount of sleep actually obtained<br>Complaint of wakefulness in spite of sleep studies showing normal amounts of sleep<br>Altered sleep/wake system | Extreme subjective sleep disturbance without objective corroboration |
| Inadequate sleep hygiene | Frequent napping/irregular sleep schedule<br>Regular use of caffeine, alcohol, tobacco, or other drugs close to bedtime<br>Regularly engaging in mentally, physically, or emotionally stressful activity before bedtime<br>Using the bed for activities other than sleep or sex (e.g., reading, television, video games)<br>Inappropriate pre-sleep and sleep environment (e.g., too hot, excessive light, too loud or quiet) | Inability to initiate sleep<br>Chronic sleep/wake difficulty |
| Behavioral insomnia of childhood (sleep-onset association type or limit-setting type) | Poor sleep training or limit setting by caretakers or parents<br>Some children are a mixed type | Child's dependence on specific objects, settings, or stimulation for initiating or returning to sleep (sleep-onset association type)<br>Bedtime stalling or refusal (limit-setting type) |

*Source: [2]* *Table 1*

Although these subtypes are discussed in the ICSD-3-TR, a diagnosis of chronic insomnia disorder should be made for all adult and pediatric patients who have a complaint of persistent and frequent insomnia, despite the absence or presence of a comorbid medical disorder, psychiatric disorder, or substance abuse [2]. Given the state of knowledge and evidence regarding insomnia, this has been deemed the most justifiable approach and is more compatible with the DSM-5-TR.

**Epidemiology**

Approximately 10% of the adult population is affected by chronic insomnia disorder as defined by the ICSD-3-TR [2]. The disorder is more common in women than in men and affects a greater number of individuals with low socioeconomic status versus those who are economically and socially stable. Patients with medical, psychiatric, and/or substance abuse problems are disproportionately affected.

Older individuals are more often diagnosed with chronic insomnia, likely due to medical conditions, medications used to treat them, and age-related sleep continuity decline [2]. Transient insomnia affects 30% to 35% of the adult population.

Prevalence of insomnia in children and adolescents is estimated at 10% to 30% and 3% to 12%, respectively, with wide variance due to definitions of insomnia used in research. It is more frequently diagnosed in adolescent girls than boys [2]. Although the specific ICSD-3-TR diagnosis has changed, the problems associated with childhood sleep disorders have not. Most chronic childhood insomnia cases are due to caregiver/parental behavior, bedtime interactions, and cultural influences, and the underlying difficulties are still primarily sleep-onset and/or limit-setting problems [2]. The need for and provision of nighttime contact varies among cultures, which should be taken into account. Infants do not establish a regular sleep pattern until approximately 3 to 6 months of age, and an insomnia diagnosis is typically not made before 6 months of age.

### Etiology

The etiology of chronic insomnia disorder is multifactorial. A genetic predisposition to insomnia may exist in some individuals, evidenced by a familial occurrence between mothers and daughters, monozygotic twins, and, to some extent, other first-degree relatives [2]. It is not clear whether the association(s) arises from learned behavior and a shared environment, is the byproduct of a common psychopathology, or is a true genetic predisposition. Numerous medical conditions, including heart failure, chronic obstructive pulmonary disease, and major depressive disorders, are associated with high rates (25% to 50%) of insomnia. Maladaptive thinking and behaviors in response to life stresses frequently play a role in the development and persistence of insomnia. These include situational anxiety, negative expectations regarding sleep, and concerns regarding potential consequences of not sleeping well. Variability in timing of sleep-wake behaviors can lead to circadian dysregulation, and excessive time in bed may dampen the homeostatic drive for deep sleep and/or lead to conditioned arousal [149].

### Diagnosis in Adults

Chronic insomnia disorder is a clinical diagnosis based primarily on subjective reports from adult patients and objective and subjective reports for children and adolescents. A 2023 clinical review provides a pragmatic approach to screening, assessment, and diagnosis of insomnia in the primary care setting [136]. The suggested goal of the initial clinical evaluation is to characterize the sleep problem, identify factors that impact sleep, and assess level of distress and impairment of daily activities. Elements to explore include sleep schedule, sleep hygiene practices, and chronicity of the sleep problem. Inquiries should probe the time the patient goes to bed, length of time it takes to fall asleep, number of awakenings and interval required to fall back asleep, usual time of arising to start the day, and any napping during the day. In assessing sleep hygiene, it is important to inquire about pre-bedtime activities, timing of meals, and bedroom environment (e.g., sources of extraneous light and sound). Other elements in the history that may be helpful are the patient's estimated total sleep time versus expected sleep time, sleep aids or other supplements used before bedtime, and level of concern/anxiety about the sleep problem [136].

In evaluating insomnia disorder, it is important to identify any psychosocial factors, comorbidities, prescription medications, or substance use that may impact symptoms. In some patients with chronic insomnia, the differential diagnosis may include a sleep study, if warranted, but this is not needed for routine evaluation in most patients.

There are three prominent features of chronic insomnia disorder [2]. The first is frequent and persistent difficulty initiating or maintaining sleep, and this is the intrinsic essential feature of chronic insomnia disorder [2]. This repetitive failure results in the patient's general dissatisfaction with sleep and quality of life. Insomnia, though chronic, does not necessarily occur every night. Some patients will have episodes of recurrent insomnia, while others constantly struggle with sleep insufficiency. It is common for individuals with persistent insomnia to have several bad nights of sleep with an occasional

good sleep [2]. Other patients who are predisposed to insomnia may experience poor sleep in relation to stressful life events. An initial episode of acute insomnia related to a stressful event will typically resolve in most individuals as they adjust to their new reality; however, this episode has the potential to become a chronic problem for some patients. The remembrance and anticipation of insomnia following a stressful event, coupled with actual sleep difficulties and daytime impairment, can lead to a cycle of disordered sleep [2].

The second feature of chronic insomnia is worry about sleep difficulties and/or academic, family, social, vocational, or other functional impairment [2]. Patients with insomnia often display excessive preoccupation with sleep, which can be problematic. Worrying about not getting enough sleep and not being able to initiate sleep following an episode of insomnia can lead to a vicious cycle of becoming tense or agitated as bedtime approaches (with corresponding adrenaline release), trying too hard to sleep (e.g., lying in bed for extended periods of time), becoming increasingly distressed and agitated at the inability to sleep, and being further unable to initiate sleep [43].

Preoccupation with general health and wellness may predispose individuals to chronic insomnia, and repression and internalization of disturbing feelings may be a common trait [2]. It may appear that patients are overly anxious, and in fact, recurrent thoughts of poor sleep performance may trouble these individuals in the morning and afternoon and attain a peak at night. However, generalized anxiety is not the norm for chronic insomnia sufferers. Screening for comorbid general anxiety is recommended when symptoms seem to extend beyond an emphasis on disordered sleep [2]. Environmental and biologic sleep cues often become triggers for heightened sleep anxiety and arousal. For example, when the sun sets and darkness falls, thoughts of poor previous nights' sleep and sleep performance anxiety may begin. In healthy individuals, feelings of drowsiness lead to increased calm, but fatigue can cause panic and distress in those with chronic insomnia. Patients may think, "I feel tired, but I know that if I go to bed I will not be able to fall asleep," or, "I feel tired now, but I am going to feel even worse tomorrow morning when I am not able to sleep tonight." This may be, or become, true as the patient ruminates about sleep and stresses.

Subjective or objective deficits with daily functioning are noticed in individuals with chronic insomnia. These may manifest as depression, lethargy, or a desire to limit activities or work. Work productivity may suffer, as may academic performance.

Patients often readily express sleep anxiety and may acknowledge their ability to sleep normally in unfamiliar settings [2]. The lack of environmental triggers in unfamiliar environments can help prevent sleep performance worry.

The third essential feature of chronic insomnia disorder is inability to sleep and remain asleep despite plenty of time to sleep, no nighttime interruptions, an adequate sleep environment, and other sufficient circumstances [2]. Practicing sleep hygiene, or maintaining an ideal sleep environment and optimum mental/physical state to promote sleep, is discussed later in this course.

**Diagnosis in Children**

The diagnosis of chronic insomnia in children is somewhat different because of the strong influence of parental/caregiver and environmental factors on development. Parents should be questioned regarding their expectations for their child's sleep. Putting children to bed prematurely or allocating too much time in bed can cause sleep difficulties that may lead to chronic insomnia [2]. On the other hand, parents may not be implementing or enforcing regular bedtimes or may allow children to postpone bedtimes. As children develop greater language skills and seek individuality, limit setting becomes more important. Studies have also shown that parents of children who faced a life-threatening illness are less strict about enforcing bedtimes and allow their children greater leeway with sleeping (e.g., joining the adult bed upon waking) [2]. Abuse and unstable home environments are also known factors for insomnia in children and adults. Crowded homes (e.g., with extended family of many generations) are associated

| THE ICSD-3-TR DIAGNOSTIC CRITERIA FOR CHRONIC INSOMNIA DISORDER |
|---|
| A. The patient reports, or the patient's parent or caregiver observes, one or more of the following[a]:<br>1. Difficulty initiating sleep<br>2. Difficulty maintaining sleep<br>3. Waking up earlier than desired<br>4. Resistance to going to bed on appropriate schedule<br>5. Difficulty sleeping without parent or caregiver intervention |
| B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:<br>1. Fatigue/malaise<br>2. Attention, concentration, or memory impairment<br>3. Impaired social, family, occupational, or academic performance<br>4. Mood disturbance/irritability<br>5. Daytime sleepiness<br>6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression)<br>7. Reduced motivation/energy/initiative<br>8. Proneness for errors/accidents<br>9. Concerns about or dissatisfaction with sleep |
| C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (e.g., enough time is allotted for sleep) or inadequate circumstances (e.g., the environment is safe, dark, quiet, and comfortable) for sleep. |
| D. The sleep disturbance and associated daytime symptoms occur at least three times per week. |
| E. The sleep disturbance and associated daytime symptoms have been present for at least three months.[b] |
| F. The sleep disturbance and associated daytime symptoms are not solely due to another current sleep disorder, medical disorder, mental disorder, or medication/substance use. |
| [a]Reports of difficulties initiating sleep, difficulties maintaining sleep, or waking up too early can be seen in all age groups. Resistance to going to bed on an appropriate schedule and difficulty sleeping without parent or caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to a significant level of functional impairment (e.g., those with dementia).<br>[b]Some patients with chronic insomnia may show recurrent episodes of sleep/wake difficulties lasting several weeks at a time over several years, yet not meet the three-month duration criterion for any single such episode. Nonetheless, these patients should be assigned a diagnosis of chronic insomnia disorder, given the persistence of their intermittent sleep difficulties over time. |
| *Source: Reprinted with permission from American Academy of Sleep Medicine. The International Classification of Sleep Disorders-3 -TR: Diagnostic and Coding Manual. 3rd ed. Text revision. Westchester, IL: American Academy of Sleep Medicine; 2023.* *Table 2* |

with poor limit setting and negative sleep-onset cues. Children should also be carefully screened for comorbid medical and psychiatric conditions that may have gone unnoticed. The diagnostic criteria for adults and children are shown in ***Table 2***.

Subjective assessment with a sleepiness instrument, such as the Epworth Sleepiness Scale (***Table 3***), may be helpful to ascertain the patient's degree of impaired sleep, but laboratory testing to measure sleepiness (e.g., the Maintenance of Wakefulness Test) usually does not show greater sleepiness in this cohort compared with healthy individuals [44]. The Epworth Sleepiness Scale has been found to be particularly effective for identifying cases of insomnia and less useful for diagnosing other sleep disorders [45]. Sleep studies are not typically needed to make a diagnosis, but polysomnography may reveal poor sleep continuity (e.g., decreased sleep efficiency, intermittent wakefulness) and more stage 1 sleep and limited stage 3 sleep [44; 46]. As noted, many persons with insomnia sleep better outside their own bed, and overnight laboratory testing may not provide significant data. Polysomnographic results also vary considerably from night to night in these patients [44]. Polysomnography is recommended for elderly individuals, as they are more prone to having identifiable etiologies of insomnia.

| THE EPWORTH SLEEPINESS SCALE | |
|---|---|
| **Situation** | **Score[a]** |
| Sitting and reading | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| Watching television | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| Sitting inactive in a public place (e.g., a theater or a meeting) | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| As a passenger in a car for an hour without a break | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| Lying down to rest in the afternoon when circumstances permit | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| Sitting and talking to someone | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| Sitting quietly after a lunch without alcohol | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| In a car, while stopped for a few minutes in traffic | 0 = No chance of dozing<br>1 = Slight chance of dozing<br>2 = Moderate chance of dozing<br>3 = High chance of dozing |
| [a]A total score of 10 or more from the eight criteria reflects above normal daytime sleepiness and need for further evaluation. | |
| *Source: [47]* | *Table 3* |

## Treatment

Complaints of sleeplessness are common in clinical practice; many patients present with incident insomnia, not having reached the stage of a persistent sleep disorder. In such cases, initial treatment may begin with patient education, instruction in sleep hygiene, and adjunctive pharmacotherapy. Chronic insomnia disorder presents a more challenging management issue. Approximately 7 of 10 individuals with persistent insomnia struggle with insomnia after one year of treatment, and half still have insomnia three years later [2]. Complications of chronic insomnia include increased risk of depression, hypertension, work disability, and protracted use of prescription or over-the-counter sleep aids. Therefore, effective professional therapies are needed to avoid dangerous comorbidities and adverse drug effects. Additionally, managing comorbid medical and psychological conditions with sleep-disrupting effects is necessary for these patients. Specialty practice guidelines and professional organizations recommend cognitive-behavioral therapy (CBT) as first-line treatment for

persistent insomnia. Multicomponent CBT includes practical strategies for modifying sleep habits, regulating sleep-wake schedules, minimizing sleep arousal, and restoring healthy attitudes and beliefs about sleep and sleeplessness [136; 149].

### *Sleep Hygiene*

Initial management of insomnia typically centers on patient education and counseling aimed at behavior and lifestyle modification combined with instruction in effective sleep hygiene practices. Some of the foremost behaviors patients should modify or adhere to include keeping a consistent sleep schedule (i.e., going to bed at the same time each night and waking up at the same time each morning), devoting at least seven to eight hours each night to sleep, and creating and maintaining a bedtime ritual [48]. The optimum sleep time varies among individuals, but those with persistent excessive daytime sleepiness should sleep a minimum of six to eight hours.

Establishing a bedtime ritual involves deciding upon an activity or series of activities that provide conditioned sleep cues and consistently repeating those activities each night. The first part of the ritual should involve quitting challenging, engaging, or stressful tasks (e.g., paying bills, playing video games, watching television) and resolving any lingering worries (e.g., quarrels, dwelling problems). Some people find that if tasks are incomplete or issues are left unresolved, making a to-do list for the next day will help to clear their mind [48]. Next, patients should focus on relaxation for 20 or 30 minutes. During this time, they might read, listen to relaxing music, take a warm bath, or practice meditation and/or deep-breathing exercises. There are many other lifestyle modifications that can reduce the likelihood of developing a sleep disorder or can lead to a reduction of symptoms of an existing disorder. The following guidelines are all components of proper sleep hygiene and should be included as part of patient education for any sleep disorder [11; 48]:

- Large, heavy meals should be avoided late in the day, as should spicy, new, or exotic foods.
- Alcohol, caffeine, and nicotine should be avoided for at least four to six hours before bedtime. Alcohol initially acts as a sedative, but as the effect wears off, it can cause individuals to wake during the night. Chocolate, coffee, tea, and many other beverages contain caffeine and should be avoided at night.
- Long naps should not be part of a normal day. Occasional, light (30-minute) naps are permissible, but regular naps interrupt the sleep-wake cycle and can make falling asleep difficult at night. Patients should be able to remain awake throughout the day, and if this is not possible, this indicates insufficient sleep and/or a sleep disorder.
- Upon waking in the morning, individuals should seek out sunlight. Exposure to bright sunlight helps regulate the sleep-wake cycle. This is especially important for older adults and those who do not leave the house regularly.
- Patients should be encouraged to engage in at least 20 minutes of moderate-intensity exercise per day, a minimum of two to three hours before bedtime. Vigorous exercise is best performed in the afternoon or earlier in the day, while relaxing exercises (e.g., deep breathing, light yoga, meditation) may be performed before bedtime. Exercise performed earlier in the day helps deepen sleep.
- The bed should be used only for sleep and sex. Patients who do not fall asleep within 15 to 20 minutes of being in bed should get out of bed and engage in an uncomplicated or relaxing activity in low-light conditions until they feel drowsy. Taking a bath, reading, or having a small snack is recommended; watching television, doing work, or engaging in other mentally engaging activities is not. One should not lie in bed trying to force sleep.

The following changes to the sleeping environment have also been shown to promote sleep [48]:

- Keep the bedroom at a cool, yet comfortable, temperature. Use blankets rather than a heater for warmth, as cooler room temperatures lead to better sleep.
- Remove the television from the bedroom. Television programs and commercials are designed to be engaging and/or provocative and can keep individuals awake for many hours. Additionally, darkness is necessary to stimulate melatonin production, and light from the television can be disruptive if left on all night.
- Keep the bedroom as dark, quiet, and relaxing as possible. Ensure that bedding is comfortable. Use an eye shade or thick curtains to block out early morning sunlight, streetlights, and headlights. Some people find earplugs useful, and others use white noise or other machines to block out aberrant sounds.

A sleep hygiene regimen is a universally applicable prevention and treatment strategy that can improve sleep quality for those with and without a specific sleep disorder. Most sleep experts recommend that sleep hygiene be used as an adjunct to treatment for sleep disorders [2]. Despite limited research supporting the role of proper sleep hygiene in patients with insomnia, many patients will find these suggestions helpful. It has been found that individuals with chronic insomnia who are highly aware of poor sleep hygiene practices may be the most indifferent toward making changes [2].

### *Cognitive-Behavioral Therapy and Other Modalities*

Many patients with chronic insomnia respond poorly or relapse despite simple nonpharmacologic and brief sedative-hypnotic modes of treatment. In 2021, the AASM published an updated clinical practice guideline that addresses behavioral and psychological interventions for treatment of chronic insomnia disorder [149]. The guideline is based on a systematic review and meta-analysis of clinical studies referencing therapeutic modalities in common usage, including CBT, sleep restriction, stimulus control, and relaxation training. These treatment modalities are designed to reduce and eliminate the common factors that perpetuate insomnia. Each therapeutic intervention was assigned a strength ("strong" or "conditional") relative to quality of the evidence supporting efficacy. A "strong" recommendation signifies a therapy that clinicians should follow under most circumstances. A "conditional" recommendation is one that advises the use of clinical knowledge and experience in combination with the patient's values and preferences to determine the best course of action [149]. Multicomponent CBT received a "strong" recommendation; all other (single-mode) interventions a "conditional" recommendation.

Multicomponent CBT, utilizing stimulus control, relaxation training, and sleep restriction therapies, sequentially or in combination, achieves the best results [46; 49]. The course of treatment typically requires four to eight sessions and includes sleep hygiene instruction, relaxation training, and other counter-arousal techniques [149]. Stimulus control therapy, which is akin to maintaining strict sleep hygiene, has been extensively studied and is the most recommended modality for initial insomnia treatment [43]. However, because sleep cues and other practices learned with sleep hygiene/stimulus control may become (or may already be) a cause of arousal, it is unlikely that all clinical subtypes will benefit significantly from this form of therapy.

The effectiveness of CBT for psychophysiologic insomnia has been demonstrated in multiple clinical studies [43; 49; 50; 51; 149]. Accessible CBT programs are available in individual, group, telephonic, web-based, and self-help bibliotherapy contexts. Patients also tend to prefer CBT over pharmacologic options and other forms of psychotherapy [51].

Relaxation techniques (e.g., biofeedback, breath counting/deep breathing, meditation, progressive relaxation) can be an effective adjunct to CBT [46; 52]. Progressive relaxation can be particularly effective in somatic-sensitive patients who tend to transform stress into physical tension. This form of therapy involves tensing and relaxing individual muscle groups while breathing deeply, starting from the toes, working progressively through the calves, thighs, stomach, shoulders, hands, arms, and neck, and ending with the facial muscles. Deep breathing exercises use slow, controlled breaths (while counting) to "quiet" racing thoughts; if the mind wanders from counting breaths, patients should resume counting and eventually they should fall asleep [52].

Sleep restriction is also a useful form of therapy [52; 53]. This technique is used to optimize the sleep drive and regain healthy circadian rhythm, based on the observation that deeper, more consolidated sleep occurs in sleep-deprived test subjects. Through this paradoxical approach, patients learn to associate time spent in bed with time spent sleeping [54]. The first step is for patients to keep a sleep log for two weeks to determine their average total sleep time (i.e., average amount of time asleep in bed); 30 minutes is added to this time to establish the time they will be allowed in bed [55]. For example, if the patient's average total sleep time is 5 hours, the allowed time in bed will be 5.5 hours. Next, a wake time is set based upon when the patient needs to start their day (e.g., 6:30 a.m.), and the bed time is set by counting backward based on the time in bed allowance (e.g., 1:00 a.m.). Regardless of how sleepy the patient feels, he or she must not nap or get into bed before the prescribed bedtime. Upon waking, the patient should expose his or her eyes to bright light (daylight whenever possible) to reinforce the sleep/wake cycle [55]. If after two weeks the patient feels tired during the day, they may add 15 minutes to the sleep allowance, and every successive week they may add an additional 15 minutes until they are able to get to sleep easily, are sleeping well throughout the night, and feel rested during the day [55]. The minimum amount of sleep needed to achieve these goals is recommended, and a consistent sleep and wake time must be maintained. This therapy should be discontinued if job performance or safety is compromised due to excessive daytime sleepiness.

### *Pharmacologic Options*

For some patients, CBT in combination with a pharmacologic agent, administered over six to eight weeks, is an effective strategy. The primary pharmacologic option for patients with chronic insomnia disorders is a sedative-hypnotic drug (e.g., eszopiclone, ramelteon, triazolam, zaleplon, zolpidem) or a mildly sedating antidepressant (e.g., doxepin) administered before bedtime. However, long-term treatment with sedative-hypnotics is associated with a high rate of adverse effects, including cognitive impairment, constipation, dizziness, headache, heartburn, the development of parasomnias (e.g., sleepwalking, sleep driving), and reduced respiratory drive [50]. When used, the lowest effective dose is recommended to reduce the likelihood of adverse effects [50]. Additionally, AASM guidelines for the pharmacologic treatment of chronic insomnia in adults provide "weak" recommendations for the agents reviewed. AASM emphasizes that this grade does not indicate that the agents are ineffective but rather reflects a "lower degree of certainty in the outcome and appropriateness of the patient-care strategy for all patients" [56]. Patients should be cautioned not to combine these medications with alcohol or other central nervous system (CNS) depressants, as their combination can cause increased liver toxicity and drastically reduced cognitive and psychomotor functioning [57]. Strategies that employ prescription medication are considered second-line treatment for insomnia disorder and should be used on a time-limited basis when CBT is either unsuccessful or unavailable [136].

Different sedative-hypnotics are indicated for various sleep difficulties. Zaleplon is fast acting, but has a short half-life; this drug may be best for patients who experience night awakenings with difficulty returning to sleep [58]. Zolpidem has a rapid onset and short-half life as well; patients with difficulty falling asleep may benefit from this drug. A controlled-release version is also available. Eszopiclone has a slow onset and long duration of action and is indicated for patients with difficulty staying asleep and with perception of poor sleep quality [57].

The American Academy of Sleep Medicine recommends the following agents be considered for the treatment of chronic sleep-onset insomnia:

- Eszopiclone
- Zaleplon
- Zolpidem
- Triazolam
- Temazepam
- Ramelteon

(https://jcsm.aasm.org/doi/10.5664/jcsm.6470. Last accessed December 16, 2024.)

**Strength of Recommendation**: Weak (A lower degree of certainty in the outcome and appropriateness of the patient-care strategy for all patients)

Hypnotic drugs are best utilized when nonpharmacologic measures do not achieve symptom reduction, when insomnia causes serious impairment, or when an immediate response is desired [54]. The following are best practice guidelines regarding the prescription and use of sedative-hypnotics [54; 59]:

- Avoid these agents or exercise caution if patient has a history of substance abuse, acute cerebrovascular accident, myasthenia gravis, or respiratory impairment.
- Prescribe hypnotics only for short durations (one to two weeks) and intermittently (based on symptom resolution).
- Watch for requests for escalating doses or resistance to tapering/discontinuing hypnotic.
- Hypnotics should be discontinued gradually. Be alert for adverse effects (especially rebound insomnia) and withdrawal phenomena when titrating doses.
- The lowest effective dose should be prescribed.

### *Herbal and Hormonal Supplements*

A variety of herbal, hormonal, and dietary supplements have been marketed as sleep aides, with scant evidence of significant benefit. Melatonin, a brain hormone produced by the pineal gland, does have some function in regulating the normal sleep cycle, and melatonin supplementation may be of benefit to a subset of patients with delayed sleep phase syndrome (a disturbance of the circadian rhythm). However, it does not appear to be helpful for most people who have insomnia. It is safe when used in modest dosage (2–3 mg per night) for short periods (three months or less) [60]. Melatonin is unregulated by the U.S. Food and Drug Administration (FDA); formulations vary in strength, and higher doses can lead to adverse side effects (e.g., disrupted sleep, fatigue, headache) [57]. AASM does not recommend melatonin for sleep onset or sleep maintenance insomnia in adults [56].

Valerian is a popular herbal product commonly used to self-treat insomnia. It causes CNS sedation by inhibiting the breakdown of certain chemical mediators within the brain. Clinical trials have shown minimal effectiveness at best [61]. This product is also unregulated by the FDA. Daytime drowsiness and rare instances of liver toxicity have been observed in association with its use. AASM does not recommend valerian for sleep onset or sleep maintenance insomnia in adults [56].

### SHORT-TERM INSOMNIA DISORDER

The essential features and diagnostic criteria of short-term insomnia disorder are similar to those of chronic insomnia disorder, minus the frequency and duration criteria. Insomnia is considered short-term if lasting fewer than three months [2; 46]. The differential diagnosis should exclude circadian rhythm sleep-wake disorders caused by jet lag or rotating shift work. These are caused when the established circadian rhythm is decoupled from the normal sleep-wake schedule. Individuals with short-term insomnia experience sleep difficulties within their normal sleep-wake schedule.

Approximately 15% to 20% of individuals experience short-term insomnia each year [2]. The frequency is higher in women than in men and in older age groups. Although many cases of short-term insomnia resolve over time or when the stressor is removed, a significant number of cases progress to chronic insomnia, as discussed. Treatment of short-term insomnia should focus on good sleep hygiene, but CBT and pharmacotherapy may be warranted in order to ensure non-progression to chronic insomnia [46].

## SLEEP-RELATED BREATHING DISORDERS

As the name suggests, the ICSD-3-TR category of sleep-related breathing disorders includes any respiratory disorders that occur during sleep. This category is further organized into the following subgroups and disorders [2]:

- Obstructive sleep apnea syndromes (adult and pediatric) caused by upper airway obstruction.
- Central sleep apnea syndromes, which are caused by cardiac or nervous system dysfunction. The eight disorders in this group are:
  - Central sleep apnea with Cheyne-Stokes breathing
  - Central apnea due to medical condition without Cheyne-Stokes breathing
  - Central sleep apnea due to high altitude periodic breathing
  - Central sleep apnea due to a medication or substance
  - Primary central sleep apnea
  - Primary central sleep apnea of infancy
  - Primary central sleep apnea of prematurity
  - Treatment-emergent central sleep apnea
- Sleep-related hypoventilation disorders, including obesity hypoventilation syndrome, congenital central alveolar hypoventilation syndrome, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep-related hypoventilation due to medication or substance, and sleep-related hypoventilation due to a medical disorder
- Sleep-related hypoxemia disorder, including sleep-related hypoxemia
- Isolated symptoms and normal variants

Only obstructive sleep apnea syndrome will be discussed in detail in this section, as the other sleep-related breathing disorders are comparatively rare and/or mainly associated with other medical conditions. For example, central sleep apnea due to Cheyne-Stokes breathing is primarily associated with congestive heart failure and stroke, and primary central sleep apneas of infancy or prematurity are associated with premature birth and low birth weight, occurring in 25% of infants weighing <2,500 g and 84% of infants weighing <1,000 g [2]. Others are extremely rare. It is estimated that there are perhaps a total of 200 congenital central alveolar hypoventilation syndrome cases worldwide [2].

## OBSTRUCTIVE SLEEP APNEA SYNDROME

Obstructive sleep apnea syndrome is characterized by recurrent upper airway obstruction caused by repetitive narrowing or collapse of the pharyngeal airway during sleep, resulting in reductions (hypopneas) or pauses (apneas) in breathing, in spite of abdominal and chest movements; reduced blood oxygen saturation (less than 50% in some patients); and frequent arousals (potentially hundreds per night) [2; 62]. Loud snoring coupled with periods of silence lasting at least 10 seconds, but often 20 to 30 seconds, are features of the syndrome. Gasping may occur instead of snoring, especially in children and adolescents; however, most patients with obstructive sleep apnea begin loud snoring in childhood. Patients may have grown accustomed to the excessive sleepiness, mental dullness, depression, frequent night awakenings, dry mouth, and morning headaches that accompany the disorder [2]. Alcohol use can increase snoring intensity, as can excess weight gain and obesity. Patients with obstructive sleep apnea often have nasopharyngeal abnormalities [2]. Adult patients typically have a generalized narrowing of the upper airway, and enlarged adenoids and/or tonsils are commonly seen in children.

Individuals may experience bouts of acute obstructive sleep apnea as the result of an inflammation-causing illness (e.g., Epstein-Barr virus, upper respiratory infection) or as a result of the ingestion of alcohol, drugs, or medications that cause relaxed muscle tone (especially in the genioglossus and geniohyoideus muscles). Individuals with occasional symptoms do not typically seek or need extensive evaluation or care for sleep apnea other than treatment for a primary condition or cessation of the substance causing airway restriction [2]. On the other hand, patients for whom the disorder is chronic (i.e., six months or longer) require careful evaluation and prompt initiation of treatment, as even mild cases of chronic obstructive sleep apnea have been consistently and independently linked to cardiac arrhythmias, cardiovascular disease, hypertension, stroke, motor vehicle accidents, and diminished quality of life [63; 64].

If a patient presents with complaints of excessive daytime sleepiness or non-restful sleep and a history of snoring, obstructive sleep apnea should be suspected. A comprehensive medical history and physical evaluation should be obtained, and various objective sleep studies (e.g., polysomnography, portable monitors, MSLT) should be completed to confirm the diagnosis. The AHI scale has been developed to quantify and standardize the degree of obstructive sleep apnea severity. The score is determined by adding the number of apnea and hypopnea events during a patient's overnight sleep study, dividing the total number of events by the minutes of sleep, and finally multiplying the result by 60. For example, if a patient sleeps 8 hours (480 minutes) and has 120 apnea events and 80 hypopnea events (200 total events), the calculation for this patient would be 200 events ÷ 480 minutes × 60, for an AHI score of 25. A normal cutoff for AHI has never been defined in an epidemiologic study of healthy people. Most sleep centers use a cutoff of 5 to 10 episodes per hour. The severity of obstructive sleep apnea is arbitrarily defined and differs widely between centers. Recommendations for cutoff levels on AHI include 5 to 15 episodes per hour for mild, 15 to 30 episodes per hour for moderate, and more than 30 episodes per hour for severe [65]. In the example, the patient has an AHI score of 25, or moderate obstructive sleep apnea.

### Epidemiology

Obstructive sleep apnea is by far the most common sleep-related breathing disorder [62]. Using the AASM criteria, it is estimated that 1 in 5 American adults has at least mild obstructive sleep apnea and 1 in 15 has at least moderate obstructive sleep apnea [63]. The incidence of the disorder increases with age, and it is two to three times more common in men than in women [62; 63; 66]. The estimated incidence among various age-groups is [62; 66]:

- Children: 2% to 8% among both sexes
- 30 to 60 years of age: 4% to 9% of women, 9% to 24% of men
- 65 to 99 years of age (with an AHI greater than 10): 56% of women, 70% of men

Differences in incidence among racial and ethnic groups have not been extensively studied. Although race is thought to be an important risk factor for sleep disordered breathing, at this time it is not certain what role race or ethnicity plays in the development of obstructive sleep apnea. Researchers have attempted to link occurrence of the disorder to racial craniofacial differences and variations in body mass trends or fat distribution, with little replicable data to support their hypotheses [66]. Again, this may be due to a lack of research that accounts for race in the United States and other Western countries and limited research of the disorder in Africa, Asia, and the Pacific Islands.

**Risk Factors**

Many risk factors have been theoretically linked to obstructive sleep apnea. The most widespread factors are alcohol consumption, smoking, overweight and obesity, and hormonal changes related to pregnancy, menopause, and polycystic ovary syndrome [63]. There are conflicting studies for each of these theories, and only overweight and obesity is considered a statistically significant risk factor.

Excess body weight is the strongest risk factor for obstructive sleep apnea in the general population, and most (though not all) patients who present with the disorder are heavier than normal weight [2]. The overweight and obesity epidemic in the United States has caused a concurrent rise in the prevalence of sleep disordered breathing, but the mechanisms involved are still unclear [67]. Hypotheses for the pathophysiology of overweight and obesity in the disorder include distorted upper airway structure and function (caused by altered neck morphology), an altered relationship between respiratory drive and load compensation, and intensification of apnea/hypopnea events through obesity-related decreases in functional residual capacity and increased whole-body oxygen demand [63; 68; 69]. Other obesity-related conditions, including insulin resistance, generalized inflammation, hypoactive hypothalamic corticotropin-releasing hormone neurons, and visceral adiposity, have been suggested as factors in the development of obstructive sleep apnea following excessive weight gain [70]. Individuals with an "apple-shaped" body (i.e., central adiposity) or who have a greater neck circumference are thought to be more affected than those who are "pear shaped" (i.e., gynoid adiposity), but there is little concrete evidence to support this idea [67].

Obesity may also be a risk factor for obstructive sleep apnea in children and adolescents. One study found a relative risk 4.59 times higher in obese children 2 to 18 years of age compared with normal weight controls [71].

Despite the lack of consensus regarding the role of excess body weight in the pathogenesis of obstructive sleep apnea, studies have shown a strong positive correlation between body mass index (BMI) and AHI [63; 68; 72]. A decade-long Wisconsin study of 690 randomly selected participants (mean age: 46 years) found that a 10% weight gain yielded a six-fold increase in the odds of developing moderate-to-severe sleep disordered breathing compared with individuals who maintained a steady weight [67]. Those who lost 10% of their initial weight during the study period lowered their AHI score by an average of 26% (range: 18% to 34%). Several small-scale studies have shown improvements in obstructive sleep apnea symptoms following surgical weight-loss interventions. Body mass reduction following bariatric surgery can cause the most dramatic (though possibly short-term) decrease in AHI score [63; 64; 68; 72].

## Evaluation and Diagnosis

### *History and Physical Examination*

The diagnosis of obstructive sleep apnea is usually made in one of three settings: a general, routine health evaluation, a screening of high-risk patients, or an evaluation suggestive of obstructive sleep apnea [41]. High-risk groups include individuals who are obese or are being evaluated for bariatric surgery; those with atrial fibrillation, congestive heart failure, treatment-refractory hypertension, nocturnal dysrhythmias, pulmonary hypertension, type 2 diabetes, and/or stroke; and high-risk driving populations (i.e., commercial truck drivers). During the initial evaluation, a history of snoring and daytime sleepiness should be taken, along with an assessment of BMI, blood pressure, maxillofacial irregularities (e.g., retrognathia), and upper airway restriction (e.g., large adenoids/tonsils).

A detailed sleep history should be obtained, including evaluation for [41]:

- Snoring
- Witnessed apneas
- Gasping/choking episodes
- Excessive sleepiness not explained by other factors, including assessment of sleepiness severity by the Epworth Sleepiness Scale
- Total sleep amount
- Nocturia
- Morning headaches
- Sleep fragmentation/sleep maintenance insomnia
- Decreased concentration and memory

Any of the previously discussed complications associated with obstructive sleep apnea (e.g., hypertension, stroke, motor vehicle accidents) should be documented. The physical examination may reveal common physical traits associated with obstructive sleep apnea, including [41]:

- Increased neck circumference (>17 inches in men, >16 inches in women)
- BMI ≥30
- Large tongue (modified Mallampati score of 3 or 4)
- Lateral peritonsillar narrowing
- Tonsillar hypertrophy
- Elongated/enlarged uvula
- High arched/narrow hard palate
- Nasal abnormalities (e.g., deviation, polyps, valve abnormalities, turbinate hypertrophy)
- Retrognathia
- Overjet (protrusion of the upper teeth)

The differential diagnosis of obstructive sleep apnea in adults includes nonpathologic snoring, panic attacks, laryngospasm related to gastroesophageal reflux, and dyspnea associated with pulmonary edema [2].

### *Testing*

Objective testing with a standardized method follows suspicion of obstructive sleep apnea to confirm the diagnosis and guide the initiation of treatment. In-laboratory polysomnography is the preferred method of objective sleep testing and is recommended for most patients [41]. At-home testing with portable monitors may be used prior to laboratory testing or to confirm the efficacy of treatments, but it should not be used for individuals with a high degree of comorbidity unless in-laboratory monitoring is not feasible due to safety or mobility issues.

The American Academy of Sleep Medicine recommends that if a single home sleep apnea test is negative, inconclusive, or technically inadequate, polysomnography be performed for the diagnosis of obstructive sleep apnea.

(https://aasm.org/resources/clinicalguidelines/diagnostic-testing-osa.pdf. Last accessed December 16, 2024.)

**Strength of Recommendation**: Strong (Should follow under most circumstances)

### *Diagnostic Criteria for Adult Patients*

The AASM has established diagnostic criteria for adults suspected of having obstructive sleep apnea. In all cases, the disorder must not be better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder. In addition, patients must display the following signs and symptoms [2]:

- Polysomnographic recording or out of center sleep testing showing 15 or more predominantly obstructive respiratory events (i.e., apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep

OR

- Polysomnographic recording or out of center sleep testing showing five or more predominantly obstructive respiratory events per hour of sleep
- At least one of the following:
  - Complaints of daytime sleepiness, fatigue, insomnia, or other symptoms leading to impaired sleep-related quality of life
  - Waking with breath holding, choking, or gasping
  - Bed partner or observer reports loud snoring, breath interruptions, or both

### *Diagnostic Criteria for Pediatric Patients*

The criteria established to diagnose obstructive sleep apnea in adults have been found to be insufficient to identify children with the disorder. For these patients, parents or caretakers must report a history of labored breathing, snoring, or both, and observation of at least one of the following must be made to diagnose pediatric obstructive sleep apnea [2]:

- Snoring
- Labored, paradoxical, or obstructed breathing during sleep
- Sleepiness, hyperactivity, behavioral problems, or learning and other cognitive problems

Differentiating obstructive sleep apnea from primary snoring requires the use of polysomnography. Further, one (or more) scorable event per hour must be recorded during the sleep study. For diagnosis of obstructive sleep apnea in children, polysomnographic findings must include [2]:

- One or more obstructive apneas, mixed apneas, or hypopneas, per hour of sleep

OR

- A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia ($PaCO_2$ >50 mm Hg) in association with one or more of:
  - Snoring
  - Flattening of the inspiratory nasal pressure waveform
  - Paradoxical thoracoabdominal motion

The disorder must also not be better explained by any other medical condition, including another sleep disorder, or medication or substance use.

### Treatment

Due to the chronic nature of the disorder, obstructive sleep apnea treatment is typically long-term and includes behavioral, medical, and surgical options. Patient education regarding the clinical consequences, natural history, pathophysiology, and risk factors of the disorder, and general information, such as alcohol avoidance, risk factor modification, medication effects, weight loss, sleep position, and drowsy driving, should be given upon diagnosis. The goals of treatment are to improve breathing during sleep, to lessen or prevent the sequelae associated with excessive daytime sleepiness and the disorder itself, and patient and partner satisfaction [41].

### *Positive Airway Pressure Therapy*

According to the American College of Physicians (ACP), the principal initial treatment for obstructive sleep apnea is positive airway pressure (PAP) therapy, which uses forced air to maintain a patent pharyngeal airway [73]. This therapy may be provided in one of three modes: continuous (CPAP), bilevel (BPAP), or autotitrating (APAP), all with or without pressure relief (i.e., partial pressure reduction during expiration) [41; 71]. CPAP is the standard mode of PAP therapy; BPAP and APAP are used when CPAP cannot be tolerated. CPAP therapy is also recommended for patients with mild obstructive sleep apnea who have failed to improve with behavior modification or who are unable to enact lifestyle changes and who have symptoms that affect their ability to perform daily tasks and impact their quality of life [71].

CPAP appliances consist of a mask or other device that fits over the nose or the nose and mouth, a tube that connects to the mask, and a motor that blows air into the tube [74]. A humidifier and/or heater can be used to condition the device air and lessen or prevent complications, such as throat irritation, nasal dryness, and nasal bleeding. Many patients have difficulty adjusting to wearing the mask and may feel confined during sleep. Periodically wearing the mask during the day, trying CPAP while awake, or using relaxation exercises should be recommended to help in getting comfortable with the device [74]. Newer machines have a "ramp" feature that slowly builds to the prescribed pressure level, which can help with adjusting to the unnatural feeling that CPAP can create.

The clinical effectiveness of CPAP therapy on measures of self-reported daytime sleepiness, fatigue, cognitive function, and depression is supported by evidence. However, the effect on other measures, such as hypertension and cardiovascular events, is unclear [74]. A 2012 clinical trial summary showed that 19% of patients in the CPAP study group developed hypertension, compared with 22% in the control group (dietary and sleep hygiene counseling), and 8% of patients using CPAP had a cardiovascular event, compared with 8% in the control [75]. Although the authors stated that CPAP therapy outcomes failed to reach statistical significance in reduction of these two measures, the small study size may have had limited power to detect a significant difference. A meta-analysis that included 3,780 patients found that, compared with medical therapy alone, CPAP was not associated with a reduced risk of major adverse cardiac events. Improved cardiac outcomes were observed only in a subgroup of patients who wore the CPAP mask for more than four hours at a time [76]. A 2021 meta-analysis that included 2,590 participants found a significant association between use of CPAP and reduced risk of major adverse cardiovascular events, particularly among participants with an AHI less than 30 events per hour [77]. Still, the authors concluded that more research is needed to confirm this benefit.

### *Oral Appliances*

An oral appliance is a custom-fit, molded mouthpiece that is fitted by a dental professional to enlarge the upper airway and/or decrease upper airway collapsibility. There are two types of oral appliances: mandibular advancement devices (MADs), which advance the mandible with respect to the resting position and cover the upper and lower teeth, and tongue-retaining devices, which do not reposition the mandible but hold the tongue forward relative to the resting position. The ACP recommends MADs as an alternative for patients who cannot tolerate or would prefer not to use PAP therapy [73]. A complete dental history and dental examination for appraisal of characteristic patterns of wear from nocturnal bruxism; soft tissue, periodontal, and temporomandibular joint (TMJ) assessment; evaluation of occlusion; and resolution of dental pathology precludes the fitting of the appliance. The type employed will be based on a patient's individual anatomy, preferences, and dental assessment. MADs require satisfactory jaw range of motion, no important TMJ disorder, and enough healthy teeth upon which to seat the oral appliance.

The American Academy of Sleep Medicine recommends sleep physicians consider prescription of oral appliances, rather than no treatment, for adult patients with obstructive sleep apnea who are intolerant of CPAP therapy or prefer alternate therapy.

(https://jcsm.aasm.org/doi/10.5664/jcsm.4858. Last accessed December 16, 2024.)

**Level of Evidence**: Moderate

A Cochrane Database review found that oral appliances had similar effectiveness on self-reported outcome measures (e.g., subjective sleepiness, depression) as CPAP therapy but were inferior in reducing respiratory disturbances among most patients [78]. Patients expressed a strong preference for the oral appliances. However, participants were more likely to withdraw on oral appliances than on CPAP therapy. Oral appliance therapy is recommended for patients with mild obstructive sleep apnea who fail behavioral treatments or for patients with mild-to-moderate obstructive sleep apnea who prefer the option over CPAP, who are not candidates for CPAP, or who do not respond to CPAP, or for those carefully selected patients in whom they are as effective in reducing daytime symptoms and AHI score [41; 78].

### *Behavior Modification*

There have been no large-scale clinical trials of dietary, exercise, medication, or surgical weight-loss interventions on outcomes in patients with sleep disordered breathing. However, the ACP recommends that all overweight and obese patients diagnosed with obstructive sleep apnea be encouraged to lose weight [73]. Many small-scale studies have shown that BMI reduction (by any means) is effective at reducing the number and duration of apnea and hypopnea events [64]. Other behavioral options include positional therapy and avoidance of alcohol and sedative drugs.

A 10% weight loss can considerably reduce the total number of obstructive events per night, and all patients should be strongly encouraged to achieve a BMI ≤25 through a combination of diet and exercise to improve obstructive sleep apnea symptoms and lessen the risk of comorbidities [41; 67]. Subsequent to body mass reduction, AHI should be reassessed using in-lab polysomnography to determine whether PAP adjustments are needed or if PAP therapy may be discontinued altogether. Because significant and lasting weight reduction is typically not achieved by most patients, especially with a dietary component alone, other treatment strategies should be employed simultaneously [41]. Even sustained weight loss does not often fully alleviate the disorder.

A supine sleep position is most likely to affect breathing, and maintaining a non-supine position throughout sleep helps to keep the airway patent in some patients [41]. Identification of individuals who have a low AHI in a non-supine position is necessary before positional therapy is initiated. If appropriate, a device (e.g., alarm, backpack, tennis ball, pillow) may be employed to keep the patient from sleeping on his or her back.

### *Surgical Treatment*

Before the widespread use of PAP therapy, surgery was the primary treatment for obstructive sleep apnea, and it is still indicated for certain cases. Many surgical options involving reconstruction (or bypass) of the upper airway can be used to reduce the severity of obstructive sleep apnea symptoms and increase the effectiveness of behavioral and medical treatments (***Table 4***); however, it is beyond the scope of this course to cover the details of each procedure. Bariatric weight-loss surgery is also considered a treatment for obstructive sleep apnea and is indicated for patients with a BMI ≥40 or BMI ≥35 with significant comorbidities and failure to achieve weight loss with diet and exercise [41].

| COMMON SURGICAL PROCEDURES FOR OBSTRUCTIVE SLEEP APNEA BY SITE | |
|---|---|
| **Site** | **Procedure** |
| Upper airway | Tracheotomy |
| Nasal | Septoplasty<br>Functional rhinoplasty<br>Nasal valve surgery<br>Turbinate reduction<br>Nasal polypectomy<br>Endoscopic procedures |
| Oral, oropharyngeal, and nasopharyngeal | Uvulopalatopharyngoplasty and variations<br>Palatal advancement pharyngoplasty<br>Tonsillectomy and/or adenoidectomy<br>Excision of tori mandibularis<br>Palatal implants |
| Hypopharyngeal | Tongue reduction<br>Partial glossectomy<br>Radiofrequency ablation<br>Lingual tonsillectomy<br>Tongue advancement/stabilization<br>Genioglossus advancement<br>Hyoid suspension<br>Mandibular advancement<br>Tongue suspension |
| Laryngeal | Epiglottoplasty<br>Hyoid suspension |
| Global airway | Maxillomandibular advancement<br>Bariatric surgery |
| *Source: [41]* | *Table 4* |

After a diagnosis of obstructive sleep apnea has been established, it should be determined if patients are appropriate candidates for surgery as a primary, secondary, or adjunct treatment [79]. Candidates should also be screened for comorbidities that would affect the outcome of surgery. This and individual anatomy will dictate which option is chosen. Patients with obstructive sleep apnea who have gross anatomic abnormalities that are correctable (e.g., tonsillar and/or adenoidal hypertrophy, collapse or narrowing of the retropalatal or retrolingual areas) should be considered for primary surgical treatment regardless of the severity of the disorder [41]. Surgery as secondary treatment should be considered for patients who have failed to improve with PAP therapy or with an oral appliance or who cannot tolerate either modality. Upon examination of the upper airway, a patient with a gross obstruction that is deemed likely to interfere with the placement, effectiveness, or tolerance of either oral appliances or PAP should be considered a candidate for surgery as an adjunct treatment [41].

The goals, benefits, risks, complications, and possible side effects of the chosen procedure(s) should be discussed, and the willingness to undergo surgical therapy should also be assessed. Although certain procedures (e.g., maxillomandibular advancement, radiofrequency ablation) seem to be effective in reducing AHI score, evidence for most procedures is of low quality and long-term data regarding effectiveness and sequelae is not available [79]. Patients should be informed that most surgeries will not cure obstructive sleep apnea but may improve clinical outcomes (e.g., cardiovascular risk, daytime sleepiness, mortality) [41]. The exception is tracheotomy, which can completely eliminate obstructive sleep apnea but not improve blood oxygen saturation or resolve other symptoms of hypoventilation syndrome. Tracheotomy for obstructive sleep apnea is typically only performed when all other options have been exhausted, when clinically urgent, or in special populations (e.g., patients with Alzheimer disease, Down syndrome, or mental and physical handicaps), as it is a radical procedure that requires a high level of care and lifestyle modification [79].

### *Pharmacologic and Oxygen Therapies*

There are no effective pharmacotherapies for obstructive sleep apnea with the exception of medications used to treat conditions (e.g., hypothyroidism, acromegaly) that can precipitate obstructive sleep apnea or that worsen symptoms of the disorder (e.g., rhinitis) [41]. Patients with persistent daytime sleepiness (despite well-documented improvement in AHI score with PAP or other treatments) may benefit from use of the analeptic modafinil. All other causes of daytime sleepiness must be ruled out and PAP therapy should not be discontinued when taking modafinil. This drug is also used for the treatment of narcolepsy and will be discussed in detail later in this course. In 2019, two drugs, solriamfetol (Sunosi) and pitolisant (Wakix), were approved by the FDA to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea. [57; 80]. Solriamfetol, a dual dopamine-norepinephrine reuptake inhibitor, has exhibited robust efficacy in randomized controlled trials. Initial oral dosing is 37.5 mg once daily, titrated up to a maximum dose of 150 mg/day. The most common adverse reaction is headache [57]. Pitolisant is a histamine H3 receptor inverse agonist approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. Initial oral dosing is 8.9 mg once daily for one week, then 17.8 mg once daily for one week. The dose may be further increased based on response and tolerability during the third week to a maximum dose of 35.6 mg once daily. As with solriamfetol, the most common adverse reaction is headache [57]. Oxygen therapy is not considered a useful treatment for obstructive sleep apnea, as it has been found that it can lengthen the duration of apneas [41]. However, it is sometimes used to relieve hypoxemia. Resolution of hypoxemia must be documented to justify continued use, especially in patients with comorbid respiratory disease who are at an increased risk of hypercapnia with oxygen therapy.

## CENTRAL DISORDERS OF HYPERSOMNOLENCE

The ICSD-3-TR category of central disorders of hypersomnolence includes those that cause excessive daytime sleepiness as the primary complaint; circadian-rhythm shifts and disturbed nocturnal sleep must not be the cause of the primary symptom [2]. The eight disorders in this group are narcolepsy type 1 (with cataplexy); narcolepsy type 2 (without cataplexy); idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical disorder; hypersomnia due to a medication or substance; hypersomnia associated with a psychiatric disorder, and insufficient sleep syndrome [2]. For simplification, the two types of narcolepsy will be discussed as one in the following section, as will idiopathic hypersomnia, along with a brief section on other ICSD-3-TR hypersomnias.

## NARCOLEPSY

Narcolepsy is a primary disorder of the CNS characterized by recurring episodes (every two to three hours) of extreme sleepiness, sudden and irresistible sleep attacks, disturbed nighttime sleep, and memory problems resulting from sleep deficit [2; 81]. Sleep spells (or attacks) usually occur during activities or situations in which sleepiness is common (e.g., as a passenger, in a class with no participation, during movies) and last 10 to 20 minutes, on average. However, they may also occur at times when sleeping is not normal (e.g., while driving, eating, walking, or talking). Individuals will feel rested when they awake, but this sense of refreshment does not last long. Sleepiness soon returns, and the cycle repeats. The disorder strongly features SOREMPs and is associated with several pathologic REM sleep phenomena, including cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations [82].

Narcolepsy occurs in two basic subtypes: with cataplexy and without. Cataplexy is defined as a loss of bilateral muscle tone triggered by intense emotions with an exciting element (e.g., anger, elation, laughter, surprise, sexual arousal) [2; 81; 82]. All skeletal muscle groups may be involved, or the effects may be localized. Typical patterns include weakening of the eyelids, mouth, neck, waist, or upper or lower limbs. Smooth, cardiac, and oculomotor muscles are unaffected. The severity of cataplexy varies between individuals and can range from mild eye droop and slurred speech to buckling of the knees and complete postural collapse with fall. The episodes typically last from seconds to minutes. Recovery is usually immediate and complete, but episodes can be repetitive in some individuals if the emotional stimulus recurs, referred to as status cataplecticus, and in rare instances, recurrent attacks have been known to last for up to one hour [2]. Some patients experience cataplexy daily, while others may experience it less than monthly [81].

Most narcoleptic patients experience sleep paralysis, or an inability to speak or move for one to several minutes (up to one hour rarely) while transitioning into and out of sleep (hypnagogic and hypnopompic, respectively) [2; 82]. Like cataplexy, sleep paralysis is a pathologic version of REM sleep atonia and does not affect smooth, cardiac, or oculomotor muscles; however, a sensation of being unable to breathe often accompanies the episode. In cataplexy and sleep paralysis, extensor and flexor reflexes are both lost, which typically only occurs in healthy individuals during REM sleep [42]. A 2011 meta-analysis of 35 studies found that sleep paralysis is experienced by approximately 7.6% of the U.S. general population at some point in their lives, but up to 60% of patients with narcolepsy regularly experience the phenomenon [83; 84; 85]. Sleep paralysis is typically accompanied by hallucinations [82].

The hypnagogic and hypnopompic experiences (HHEs) that accompany sleep paralysis appear in three generalized categories but are overwhelmingly of the first type of hallucination, dubbed "Intruder." These hallucinations are described as a sensed evil, malevolent, or threatening presence [86; 87]. The second type, the "Incubus," is less common. Described as a demonic or alien being on/near the bed or on top of the body, it is associated with chest pressure, breathing difficulties, and/or pain. Pain is experienced by some individuals while attempting to move their limbs, and another subset may think their limbs are moving when they actually remain still (e.g., while fighting off a perceived threat) [86]. An extreme sense of dread or terror is usually felt during these two types of experiences. Individuals can misconstrue sounds and visions during HHEs (e.g., an object or a shadow may be seen as demon, but later they can reason the misinterpretation) or they may have full-blown, vivid hallucinations (e.g., interaction with beings they are convinced have an external source) [87]. Interestingly, descriptions of beings are consistent throughout history and across cultures, and it is thought that many alien, ghostly, and demonic assault, visitation, and possession incidents are derived from "Incubus"-type HHEs.

The third type, "unusual bodily experiences," is infrequently encountered and is described as a flying/floating, out-of-body, or blissful experience without a frightening component [86].

### Epidemiology

Narcolepsy is the second most common sleep-related disorder in the United States (after obstructive sleep apnea), affecting an estimated 1 in 2,000 individuals or an estimated 135,000 to 200,000 Americans [42]. Men and women are equally affected, but prevalence varies by race/ethnicity. For example, compared with the United States, narcolepsy is more common in Japan and less common in Israel. Narcolepsy with cataplexy is less common, estimated to affect 1 in 3,000 Americans [42]. The age of onset is typically between 7 and 25 years.

### Risk Factors

The causes of narcolepsy are not well known, so it is difficult to determine the influencing factors. There is a heritable component that can predispose individuals to developing the disorder. Certain gene variants of the human leukocyte antigen (HLA) complex and its receptor, T-cell receptor alpha (TCRA), are strongly associated with narcolepsy [42]. Most (though not all) narcoleptic individuals possess the HLA-DR2 or HLA-DQB1*0602 phenotype, which are risk factors for autoimmune disease. However, inflammatory markers and signs/clinical features of inflammatory processes are typically not found in narcoleptics [88; 89; 90]. This suggests that if the disorder does have an autoimmune origin, the pathology is confined to the nervous system.

Researchers believe that individuals with the implicated subtypes of HLA and TCRA are more prone to an immune system attack on hypocretin-producing neurons in the hypothalamus [42; 82]. The neurotransmitter protein hypocretin regulates appetite, feeding, and sleep patterns, including keeping brain systems from unexpectedly shutting off while awake. People with narcolepsy with cataplexy (and a certain subset of individuals without cataplexy) typically have very low levels of hypocretin, which could explain why they develop narcolepsy and also the higher rate of obesity in this population [42; 82; 91].

Though a genetic predisposition does exist, it does not fully explain development of the disorder, as most individuals with the HLA/TCRA variants do not develop narcolepsy and some narcoleptics do not possess these subtypes. In certain rare instances, tumor growth or head trauma have led to narcolepsy [42]. Other factors, including environmental toxins, stress, dietary factors, changes to the sleep schedule, and hormonal changes, likely contribute to the development of the disorder. Infectious agents have been identified as triggers for narcolepsy, particularly *Streptococcus* spp. and the H1N1 influenza virus, but it is not yet known if the infections are direct triggers or if they indirectly increase susceptibility (e.g., due to the relaxed blood-brain barrier during fever) [42].

### Diagnosis

As discussed, the most common presentation for all sleep disorders, including narcolepsy, is excessive daytime sleepiness. Cataplexy is rare without narcolepsy and is considered a positive indicator of the disorder [42]. If cataplexy is not present, all other causes of excessive sleepiness must be ruled out by collecting a thorough medical history and conducting an exhaustive clinical examination. The Epworth Sleepiness Scale can be used to identify excessive daytime sleepiness. For the diagnosis of narcolepsy to be confirmed, polysomnography and an MSLT should be performed in a sleep clinic. A polysomnographic study for narcolepsy is similar to an obstructive sleep apnea study. The MSLT will indicate shorter sleep latency periods in patients with narcolepsy compared with healthy individuals [42].

Laboratory testing may include cerebrospinal fluid (CSF) hypocretin-1 levels, but the value of this test is debated [2; 42; 92]. CSF hypocretin sampling is generally not recommended unless MSLTs are inconclusive or unavailable. This is because reduced or absent levels are usually only found in patients with cataplexy [42; 92]. Although most patients with narcolepsy without cataplexy have normal hypocretin levels, there is a subset who is deficient, including individuals with the HLA-DR2 phenotype, those at a younger age at onset, and patients with shorter mean REM latency periods [91].

## Treatment

Narcolepsy is incurable, and the loss of hypocretin in patients with cataplexy is believed to be irreversible [42]. However, there are several pharmacologic and behavioral treatment options that, when combined, can greatly reduce symptoms of the disorder and help improve patients' quality of life.

### *Pharmacologic Therapies*

Traditional drug treatment options for narcolepsy have included CNS stimulants taken during the daytime to help patients remain alert, sedatives taken at night to help patients attain more restful sleep, and tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) to help control cataplexy, sleep paralysis, and HHEs [42; 93; 94]. Certain drugs have been found to exert multiple effects; for example, modafinil, a stimulant drug used to treat daytime sleepiness, may also exert antidepressant effects by modulating serotonin transmission [95]. These drug classes are still recommended for prescription today, but the use of a single drug, sodium oxybate, to control all symptoms of narcolepsy (including cataplexy) is gaining favor following a series of successful clinical trials [94; 96; 97; 98; 99; 100]. However, due to abuse potential, access to the drug is tightly restricted [42; 57].

If a CNS stimulant is prescribed in order to combat the effects of excessive daytime sleepiness, the most common are various amphetamines and methylphenidate [42; 93]. These agents can be effective in reducing daytime sleepiness and the occurrence of sleep attacks. Amphetamines (e.g., amphetamine, dextroamphetamine, methamphetamine) have been prescribed for narcolepsy since the 1930s and, at lower dosages, act primarily by causing dopamine (and noradrenaline) release [101]. They may be prescribed at 10–60 mg/day. However, amphetamine use is associated with a number of adverse effects, including headache, insomnia, irritability, nervousness, and palpitations, and less frequently, anorexia, hyperhidrosis, nausea, orofacial dyskinesia, and psychosis [93]. Abuse of prescribed amphetamines is rare among narcoleptics, but tolerance develops in one-third of patients. Due to these risks and the proven efficacy of newer drugs, amphetamines are no longer recommended as first- or second-line therapy. Methylphenidate has similar, though milder, adverse effects and a much shorter half-life [94]. It is also prescribed at 10–60 mg/day, but it is recommended only when modafinil is insufficiently active, when modafinil must be supplemented at a specific time of the day, or in situations where maximum alertness is required [42; 92].

Modafinil, a stimulant, was approved for use in the United States in 1998 and is the treatment of choice for narcolepsy when the most serious symptom is excessive daytime sleepiness due to its efficacy, limited adverse effects, and easiness of manipulation [42; 92]. To date, researchers have been unable to determine the exact mechanism(s) of action, but modafinil is known to increase the release of monoamines (e.g., dopamine, norepinephrine, histamine) from synapses [93; 102]. Therefore, the central histaminergic and dopaminergic systems are suspected to be involved. Unlike with classic CNS stimulants, the coadministration of a dopamine antagonist only partially weakens the effectiveness of modafinil, leading researchers to describe the drug as a wakefulness promoting agent [57; 103]. The starting dose is 200 mg, and the usual effective dose is 200–400 mg taken as a single morning dose or as a split dose (first in the morning and then around noon). However, evidence of benefit with a dose greater than 200 mg/day is lacking [57]. There is a low prevalence of common side effects, including headache (13%), nervousness (8%), nausea (5%), and rhinitis, all of which are typically mild [92; 94]. More serious side effects have been noted and are mainly allergic/inflammatory reactions, including hives, rash, and swelling. Other severe dermatologic reactions have occurred, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN), prompting the FDA to issue a safety labeling change in 2007 [57]. There have been very few instances of DRESS, Stevens-Johnson syndrome, and TEN (less than 10 since 1998), and modafinil is considered a safe treatment for excessive daytime sleepiness.

For patients with excessive daytime sleepiness with poor nighttime sleep and cataplexy, the first-line treatment is sodium oxybate [92]. This drug, also known as gamma hydroxybutyrate (GHB), is a powerful sedative that has been burdened by the stigma as a party or "date-rape" drug and a performance-enhancing drug [94]. Misuse of the drug can be life-threatening, and steps should be taken to ensure no other sedatives (including alcohol), muscle relaxants, or respiratory depressants are taken concurrently and that sleep disordered breathing is not present or does not develop. Sodium oxybate is restricted and can only be prescribed by those enrolled in the Xyrem Patient Success Program and dispensed by the designated centralized pharmacy [57]. The initial dose is 4.5 g/night in two equal doses [57]. The first dose is taken sitting upright in bed just before sleep; the patient should lie down immediately after dose one; the second dose is taken 2.5 to 4 hours later. (An alarm may be necessary.) The dose can be increased by 1.5 g at two-week intervals up to a maximum dose of 9 g/night [57; 92]. Patients usually begin to improve after the first few nights, but the optimal response (even at the starting dose) can take up to 8 to 12 weeks. Adverse effects are common and include headache (9% to 37%), dizziness (8% to 37%), nausea (8% to 40%), vomiting (2% to 23%), pain (9% to 20%), confusion (3% to 17%), sleep disorder (6% to 14%), somnolence (1% to 14%), abdominal pain (3% to 11%), enuresis (3% to 17%), and urinary incontinence (<1% to 14%, usually nocturnal) [57].

Antidepressants are considered second-line agents for cataplexy and are also an effective treatment for sleep paralysis and HHEs [92]. The most potent anticataplectic drugs are tricyclic antidepressants, especially clomipramine (10–75 mg). However, these agents have the disadvantage of anticholinergic side effects. SSRIs have fewer side effects but are slightly less active [92]. Venlafaxine, a norepinephrine/serotonin reuptake inhibitor, is widely prescribed despite a lack of published clinical evidence to support its use. The same paucity of data exists for norepinephrine reuptake inhibitors (e.g., reboxetine, atomoxetine) [92]. Other pharmacologic agents are no longer recommended for use based on either a lack of clinical efficacy data or on their undesirable adverse effects and safety profiles [92].

Caution should be given when treating patients with comorbid psychiatric disorders. Sodium oxybate should not be used in patients with depression. Instead, antidepressants should be prescribed along with a referral to a psychiatrist or mental health provider [92].

### *Behavioral Therapies*

There are several lifestyle and dietary changes that may help reduce the symptoms and risks of narcolepsy, although there are no accepted behavioral treatments for cataplexy [92]. Behavior modification is useful as medications cannot ensure a consistent state of alertness in individuals with the disorder. Practicing strict sleep hygiene is important, and engaging in relaxation exercises or taking a bath before bedtime may offer a benefit [42]. Daytime napping has been shown to improve alertness and shorten reaction times [42]. Regular exercise (20 minutes/day, four to five hours before bedtime) can lead to better sleep and help prevent or reduce narcolepsy-related weight gain. Alcohol and caffeine should be avoided, especially at night.

The European Academy of Neurology, the European Sleep Research Society, and the European Narcolepsy Network recommend planned daytime naps to improve immediate subjective and objective sleepiness both in drug-naïve patients with narcolepsy and in those taking stimulant medication, at any age.

(https://onlinelibrary.wiley.com/doi/10.1111/ene.14888. Last accessed December 16, 2024.)

**Level of Evidence**: Expert Opinion/Consensus Statement

One of the major risks of narcolepsy is falling asleep while performing hazardous tasks (e.g., driving, operating machinery) or collapsing due to cataplexy at an ill-timed moment (e.g., while descending a stairway). Automobile accidents are 10 times more common in individuals with untreated narcoleptic symptoms, but when medication and behavioral therapies are being used, the accident rates are similar to healthy individuals [42]. Scheduled naps are recommended to reduce the likelihood of falling asleep unexpectedly. The Americans with Disabilities Act guarantees equal opportunity for narcoleptic students and workers, and reasonable adjustments to school and work schedules should be encouraged to accommodate periodic naps [42].

Support groups for narcolepsy are helpful for many patients. Overcoming feelings of isolation by connecting with other people with the disorder and lessening the sense of judgment by outsiders are important both for those who have just received a diagnosis and experienced patients alike. It may be difficult for individuals living in non-metropolitan areas to find a support group, and for these patients online groups can be useful. More information about narcolepsy support groups is available at https://www.narcolepsynetwork.org. The Narcolepsy Network offers meetings in several U.S. cities and hosts online support groups as well [104].

## IDIOPATHIC HYPERSOMNIA

Idiopathic hypersomnia is a rare disorder, affecting approximately 50 people per million population [105]. However, there are many potential causes of daily, unrelenting hypersomnia, and the disorder is a consideration in the differential diagnosis of several other conditions and sleep disorders. Therefore, a brief discussion is warranted.

Idiopathic hypersomnia is characterized by excessive daytime sleepiness without cataplexy and is not better explained by another disorder [2]. Most hypersomniacs have extreme difficulty waking from sleep. If naps are taken, they are usually longer than those taken by individuals with narcolepsy, and many patients experience confusion or disorientation, called sleep drunkenness, upon waking [106]. Also unlike narcolepsy, most (though not all) patients wake from naps still feeling drowsy or unrefreshed. Irresistible urges to sleep (sleep attacks) are rare with this disorder, and cataplexy is not a feature [105; 106]. Narcoleptics typically have disturbed nighttime sleep, whereas patients with this disorder do not. Unusual or inappropriate behaviors (e.g., staring, acting intoxicated) may occur in patients who do not take daytime naps.

### Diagnosis

There are many medical conditions that can cause hypersomnia, including Kleine-Levin syndrome, Parkinson disease, dementia, and post-traumatic stress disorder, all of which should be ruled out with a complete medical history, physical examination, and diagnostic workup. Standard sleep studies are used to confirm the diagnosis of idiopathic hypersomnia, including MSLT and polysomnography. The absence of multiple SOREMPs (one or fewer) during MSLT and greater time spent in slow-wave sleep during polysomnography suggest idiopathic hypersomnia [105]. On the other hand, multiple SOREMPs (two or more) are indicative of narcolepsy. In addition, polysomnography and MSLT findings should not be consistent with a diagnosis of narcolepsy type 1 or 2 in order for a diagnosis of idiopathic hypersomnia to be made [2].

### Treatment

The same array of pharmacologic options used to treat excessive daytime sleepiness in narcolepsy may be prescribed for idiopathic hypersomnia, but the level of effectiveness is typically not replicated [105; 106]. Only half of patients treated report any improvement of symptoms. In 2021, the FDA expanded approval of oxybate salts (calcium, magnesium, potassium, and sodium) to include treatment of idiopathic hypersomnia [143]. It is the first and only medication approved for this indication; all other pharmacologic options are prescribed off label. Although sleep hygiene practices are usually not helpful for idiopathic hypersomnia patients, they should be discussed because there are virtually no risks or drawbacks [105]. Patients should be advised to avoid sedative drugs and alcohol.

### OTHER HYPERSOMNIAS

Recurrent hypersomnia is characterized by periodic episodes of extreme somnolence accompanied by cognitive and behavioral disturbances lasting for days to weeks that punctuate an otherwise normal, healthy sleep pattern. During hypersomnia episodes, patients may sleep up to 20 hours per day (range: 10 hours to nearly 24 hours) [2; 107]. The average number of episodes is 2 per year, but it can occur up to 12 times per year. The most commonly known form of this disorder is Kleine-Levin syndrome, but there are other forms of recurrent hypersomnia with incomplete features of the syndrome, which may be associated with a medical disorder, psychological disorder, or medication/substance use [2]. Kleine-Levin syndrome is exceptionally rare in the United States, with fewer than 1 case per million population, although some believe this is an underestimate [107]. The prevalence is greater in individuals of Jewish descent compared with the overall population [108]. The onset of Kleine-Levin syndrome usually occurs in adolescence and follows an infection, such as a cold or influenza.

All patients with recurrent hypersomnia have various forms of cognitive impairment and altered perception during episodes [108]. Cognitive symptoms include impaired speech (94%), difficulty with concentration (91%), and memory impairment (66%). Altered perception symptoms include dream-like state (81%), derealization (66%), and hypnagogic hallucinations (42%). Many patients experience other psychological symptoms, including eating behavior disorders (95%), hypersexuality and disinhibition (53%), and depressed mood (53%) [108].

Recurring excessive sleepiness can occur during the premenstrual period in adolescent girls, referred to as menstrual-related hypersomnia, and is often controlled with birth-control pills [109]. This and other disorders that cause bouts of excessive sleepiness (e.g., encephalopathy, depression) should be differentiated from hypersomnia disorders.

Treatments include various stimulants, lithium, carbamazepine, and the antiparkinsonian drug amantadine, all of which have marginal efficacy [108; 109]. Hypersomnia episodes typically decrease in intensity and frequency within 8 to 12 years of onset, with eventual complete resolution common.

## CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Disorders that fall into the ICSD-3-TR category of circadian rhythm sleep-wake disorders are caused by alterations to the internal circadian timekeeping system or by environmental, physiologic, or behavioral factors that alter timing of sleep relative to an individual's circadian rhythm, leading to insomnia and/or excessive daytime sleepiness and impaired functioning [2]. Sleep timing that does not follow circadian rhythms will typically cause nonoptimal sleep. The ICSD-3-TR contains seven disorders of this type [2]:

- Delayed sleep-wake phase disorder
- Advanced sleep-wake phase disorder
- Irregular sleep-wake rhythm disorder
- Non-24-hour sleep-wake rhythm disorder
- Shift work disorder
- Jet lag disorder
- Circadian sleep-wake disorder not otherwise specified NOS

Most circadian rhythm sleep disorders are uncommon or occur in specific populations (e.g., the non-24-hour sleep-wake rhythm type in blind individuals). Jet lag and shift work disorders are related to very specific sets of conditions. Medical conditions that may be responsible for circadian rhythm abnormalities include dementia, Parkinson disease, and hepatic encephalopathy [2]. Delayed sleep-wake phase disorder affects a significant number of adolescents and young adults.

### DELAYED SLEEP-WAKE PHASE DISORDER

Delayed sleep-wake phase disorder is characterized by a habitually delayed sleep time (relative to socially acceptable or conventional sleep times) with difficulty falling asleep when others do [2]. The offset is usually more than two hours, but sleep is normal once initiated (though a late wake time is preferred if allowed). Daytime functioning is normal when individuals are allowed to sleep later, but dictated schedules cause deteriorated well-being. Depression or suicidal ideation may be the primary reason for adolescents' clinical presentation [2]. Patients with this disorder are definite "evening types."

The incidence of this disorder is unknown in the general population, but it is more common in adolescents and young adults (7% to 16%), with a mean onset of 20 years of age [2]. About 1 in 10 sleep clinic patients with chronic insomnia have a delayed sleep phase. Roughly 40% of patients with this disorder have a family member with the disorder [2].

Staying up late, with activity and indoor bright lights, can promote the disorder, as can a corresponding reduction in bright morning light [2]. Shift work, changes in schedules, and frequent travel across time zones can also precipitate the disorder. Attempts at retraining, using sleep hygiene and bright light therapy may work, but patients usually maintain a strong desire for "eveningness" despite intervention [2].

## PARASOMNIAS

In the ICSD-3-TR, parasomnias are divided into three categories: non-REM-related parasomnias (i.e., disorders of arousal from non-REM sleep), REM-related parasomnias, and other parasomnias [2]. Non-REM-related parasomnias consist of disorders of arousal, confusion arousals, sleepwalking, and sleep terrors, and sleep-related eating disorder; parasomnias usually associated with REM sleep consist of REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorder. Other parasomnias consist of exploding head syndrome, sleep-related hallucinations, sleep enuresis, parasomnia due to a medical disorder, parasomnia due to a medication or substance, and parasomnia, unspecified [2].

### SLEEPWALKING

Sleepwalking, or somnambulism, is a non-REM arousal disorder that causes individuals to walk or perform other activities while asleep. Activities may include sitting upright in bed, walking around inside/outside the house, moving furniture, getting dressed, preparing food, trying to "escape," jumping from windows, driving a car, and many others, though dangerous activities are rare [110; 111]. It is fairly common for sleepwalking children to engage in inappropriate behaviors, such as urinating in a closet or waste basket [2]. Accidents and falls may also occur, and people have even committed homicide or pseudosuicide while asleep. Patients can become violent when others attempt to awaken them from the sleepwalking episode, and most will be extremely confused if awakened and will not recall the events of the episode [110; 111].

It should be noted that sleep driving associated with *z*-drugs (e.g., zolpidem, zopiclone) and other psychiatric medications is unrelated to sleepwalking [112]. Sleep drivers will typically have some level of cognitive function (e.g., are responsive to police questioning) but will display poor balance and walking ability. Sleepwalkers, on the other hand, are perfectly able to balance while walking but have no ability to interact.

Sleepwalking typically occurs during non-REM sleep stage 3 (slow-wave sleep), which is more common early in the night (during the first-third of sleep) [110]. Episodes last an average of 10 minutes but range from a few minutes to more than 30 minutes. Patients usually return to bed before waking, but some may fall asleep in another location or awaken while sleepwalking [2]. Sleep talking may also be exhibited by these individuals, and sleep terrors may occur at other times. Sleepwalking episodes may occur frequently (several times per night, for several nights) or only rarely or when precipitating factors are present [2].

### Epidemiology

The prevalence of sleepwalking ranges from 4% in adults to 17% in children [2]. The disorder may begin as soon as a child is able to walk, but the age of onset is usually between 4 and 8 years. The disorder is most common in children 5 to 12 years of age [2; 110]. A 2004 National Sleep Foundation poll found that sleepwalking a few nights per week occurs in 1% of preschoolers and 2% of school-age children [113]. Sleepwalking is more common in children with sleep enuresis (chronic bedwetting). Symptoms of sleepwalking disappear after adolescence in most patients; however, the disorder can occur at any age [2; 110]. Approximately one-third of cases develop after adolescence [2]. Girls and boys are affected equally in childhood, but the gender distribution in adults is not well defined [2]. One study of an adult population of sleepwalkers in Nigeria found prevalence roughly three times higher in men than in women [114].

Sleepwalking may occur in isolated cases, but there is a known genetic susceptibility and a familial pattern [2; 115]. The incidence in children is 60% when both parents have the disorder and 45% when one parent is affected. The incidence is 22% if neither parent has the disorder but when sleepwalking is familial (i.e., occurs in more distant relatives) [2]. A 2012 Stanford School of Medicine study found that the self-reported yearly incidence of sleepwalking was 3.6%, equating to about 8.5 million Americans [116]. According to the study, the lifetime prevalence of a sleepwalking episode was estimated at 29.2%, with 30.5% of participants reporting a family history of the disorder. Twin studies support the role of genetic susceptibility in at least 65% of cases [2].

### Risk Factors

Although there is a strong heritable factor for sleepwalking, the pathology of sleepwalking is not known [2; 110]. Individuals who are predisposed to sleepwalking may become active sleepwalkers when priming factors exist and a precipitating factor triggers an episode [2; 115]. Priming factors deepen and increase slow-wave sleep and include anxiety, fatigue, fever, the premenstrual period, sleep deprivation, and physical or emotional stress. Alcohol use and certain medications may also be priming factors, but it is unclear if the many case reports of "sleepwalking" under the influence of substances are due to extreme intoxication or complex medication interactions (or medication/psychopathologic interactions) [2; 110; 115]. Precipitating factors, or triggers, identified in primed individuals in sleep laboratories include light, noise, periodic leg movements, sleep disordered breathing, and touch.

Certain mental disorders (e.g., obsessive-compulsive disorder) and medical conditions (e.g., organic brain syndrome, partial complex seizures) are associated with sleepwalking, as is obstructive sleep apnea [2; 110; 116]. Medication-related sleepwalking may occur, most commonly in individuals with a complex medical and psychiatric history associated with multiple medications [115]. The 2012 study found a higher risk of frequent sleepwalking episodes (two or more times/month) with obstructive sleep apnea syndrome (odds ratio [OR]: 3.9), obsessive-compulsive disorder (OR: 3.9), alcohol abuse/dependence (OR: 3.5), major depressive disorder (OR: 3.5), circadian rhythm sleep disorder (OR: 3.4), SSRI antidepressant use (OR: 3.0), over-the-counter sleep aid use (OR: 2.5), and insomnia disorder (OR: 2.1) [116].

### Diagnosis

Steps should be taken to ensure that sleepwalking is not the result of a medication side effect or an underlying medical or psychiatric condition. Specific medications and their dosages should be reviewed. In cases of pediatric sleepwalking, parents or caretakers will have witnessed one or more behaviors associated with the disorder, including [110; 111]:

- Aggressive behavior when aroused (rare)
- The appearance of being awake while still asleep
- Open eyes during sleep, with a blank look on the face
- Confusion or disorientation when roused
- Performance of detailed activities during sleep
- No memory of the sleepwalking episode
- Sleep-talking and nonsensical verbalizations

Adult patients with no history of the disorder may similarly present with no recollection of any episode of sleepwalking or associated behaviors, which may have instead been witnessed by another person. Sleep studies and other tests and procedures are typically not needed to confirm a diagnosis in patients with known good health [2; 110]. However, testing to rule out other medical conditions (e.g., partial complex seizures, obstructive sleep apnea) in patients with a limited medical history is recommended.

### Treatment

There is no cure or specific treatment for sleepwalking [110; 113]. As a first step in the management of sleepwalking, conditions or medications that may cause somnambulism should be identified and treated or discontinued, which may eliminate or greatly reduce sleepwalking episodes. For patients with sleepwalking as the primary diagnosis, identifying the priming and precipitating factor(s) is a cornerstone of management. Patients (or parents) should be instructed to keep a journal that includes daily activities, level of daytime sleepiness, total hours of sleep, and any illnesses or triggers of stress or anxiety to help to determine possible triggers, though dedication to observation and journaling lessens and more omissions occur over time [117].

Again, there is no high-quality evidence to support any specific sleepwalking treatment [113; 118]. A tailored approach to therapy, including improvements in sleep hygiene, should be made on a patient-by-patient basis. Although medication is not usually required and is not recommended as a first-line therapy, sedative-hypnotics, tricyclic antidepressants, or SSRIs may be prescribed if sleepwalking interferes significantly with the patient's or the family's quality of life (e.g., excessive daytime sleepiness, high risk of injury, unusual symptoms, inappropriate behaviors causing family distress) [110; 113]. However, the usefulness of these medications is not certain [119; 120]. Care must be taken when prescribing tricyclic antidepressants, as they have many serious side effects (especially in children) and can exacerbate sleepwalking [121]. Benzodiazepines (e.g., clonazepam, diazepam) were initially prescribed for sleepwalking, with only limited benefit [119; 120]. A 2021 review reports that benzodiazepines are effective at controlling sleepwalking [122]. One study of individuals with either isolated sleepwalking or sleepwalking related to psychiatric conditions or obstructive sleep apnea found that benzodiazepines and psychiatric medications were not effective in reducing sleepwalking episodes. Nasal CPAP therapy for participants with obstructive sleep apnea eliminated sleepwalking in all individuals who remained compliant throughout each of the follow-up periods [120].

Hypnosis has been used as a low-cost, safe therapy for various parasomnias, including sleepwalking [113; 123]. One small-scale study (27 participants) conducted by Hurwitz and colleagues showed a 74% success rate for long-term reduction of sleepwalking and night terror episodes ("much" or "very much" improvement on self-report) following one to six office visits and continued with at-home self-hypnotic exercises [124]. A five-year follow-up study of 36 parasomnia patients (modeled on the Hurwitz study) found a 45.4% success rate after 1 month (symptom free or "much improved"), which diminished slightly to 42.2% at 18 months and 40.5% at 5 years [125]. In this study, participants underwent one or two 50-minute hypnosis sessions, described as "deep physical relaxation but with retention of an active and focused mind, so possible new thoughts could be evaluated and incorporated into the hypnotized person's thinking" [125].

One behavioral approach, anticipatory awakenings, can be effective in reducing sleepwalking episodes. This method requires parents or caretakers to wake the patient three hours into the night and 15 minutes before the usual sleepwalking time. The patient is kept awake for 30 minutes and then may return to sleep. Anecdotal reports have found this intervention to be successful; however, it requires a significant commitment on the part of those involved [121; 126].

Another key to treatment is the maintenance of a safe living environment. Patient/parent education should cover precautions to be taken, including [113; 121]:

- Locking windows and doors in a way that allows for safe emergency exit
- Installing door alarms on all doors that lead outside or to a basement or attic
- Securing all potentially dangerous objects or items (e.g., tripping hazards, sharp objects, chemicals, medications, knives, guns)
- Moving the patient's bedroom to the ground floor (if possible)
- Covering windows to block out light

## SLEEP-RELATED MOVEMENT DISORDERS

The ICSD-3-TR includes 10 sleep-related movement disorder diagnoses: restless legs syndrome; periodic limb movement disorder (PLMD); sleep-related leg cramps; sleep-related bruxism; sleep-related rhythmic movement disorder; benign sleep myoclonus of infancy; propriospinal myoclonus at sleep onset; sleep-related movement disorder due to a medical disorder; sleep-related movement disorder due to a drug or substance; and; sleep-related movement disorder, unspecified [2].

### RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENT DISORDER

Although restless legs syndrome and PLMD are two distinct disorders, they are often discussed together, as they have overlapping features. PLMD is also comorbid in most (85% to 90%) patients with restless legs syndrome [2; 127].

Restless legs syndrome, also known as Willis-Ekbom disease, is a neurologic sleep disorder characterized by disagreeable leg sensations that worsen when individuals are at rest (e.g., when seated) and/or at night before bedtime [2]. There is an accompanying urge to move the legs to relieve the unpleasant sensations, which are described as aching, bubbling, creeping, crawling, pulling, searing, and/or tingling; walking, stretching, or shaking usually provides relief [128]. The area between the ankle and the knee is most often affected (usually bilaterally), but the thighs, feet, and, to a lesser extent, the arms may also be affected [2]. Pathologic changes in efficiency of central dopamine neurotransmission are thought to cause the disorder, based on the observation that restless legs syndrome symptoms are relieved by the use of dopaminergic drugs [127]. The secondary (non-idiopathic) form of restless legs syndrome can be caused by a variety of medical conditions. Iron deficiency and uremia are common causes; others include chronic kidney disease, cobalamin (vitamin B12) deficiency, folate deficiency, diabetes, fibromyalgia, Parkinson disease, peripheral neuropathy, pregnancy, radiculopathy, rheumatoid arthritis,

Sjögren syndrome, use of certain drugs (e.g., caffeine, calcium channel blockers, lithium, neuroleptics), and withdrawal from sedatives [128; 129].

Troubling and painful leg sensations that cause an irresistible urge to move initially keep patients from being able to sleep, and the discomfort is often so disrupting that patients awaken several hours after falling asleep. As such, restless legs syndrome is a significant cause of (secondary) insomnia. Periodic limb movements during sleep are very common in patients with restless legs syndrome, and involuntary limb movements occur in many patients with restless legs syndrome while awake [2]. Involuntary limb movements while awake are much less common among patients with PLMD alone.

PLMD is characterized by episodes of repetitive, stereotyped leg movements during stage 1 and stage 2 sleep, consisting of extension of the big toe in combination with partial flexion of the ankle, knee, and sometimes hip [2; 127]. The legs typically remain still during non-REM stages 3 and 4 and during REM sleep. Episodes prevail during the first half of the night and diminish progressively [129]. Intermittent flexion at the elbow may also be seen in some patients.

Some patients may not be roused by the movement episodes and only complain of excessive daytime sleepiness. However, the typical presentation is with frequent awakenings and poor sleep quality (i.e., insomnia). Bed partners' sleep is often disturbed by the movements. As with restless legs syndrome, this disorder is also thought to be caused by altered dopamine neurotransmission (based on the efficacy data of dopaminergic drugs) but can also be caused by a medical condition [127]. Certain medications can cause periodic limb movements during sleep, including tricyclic antidepressants (e.g., amitriptyline), neuroleptics and other antidopaminergic agents (e.g., haloperidol), and dopaminergic agents (e.g., carbidopa, which may be used in the treatment of PLMD).

**Epidemiology**

Approximately 5% to 15% of the adult U.S. population is affected by restless legs syndrome, and women are affected twice as often as men [2; 130]. The disorder is more common in certain groups, including pregnant women (11%), uremic patients (15% to 20%), and patients with rheumatoid arthritis (up to 30%). In general, restless legs syndrome is associated with advancing age; however, the age of onset is younger than 20 years in one-quarter of patients. Among children 8 to 11 years of age and adolescents 12 to 17 years of age, the prevalence is 1.9% and 2.0%, respectively [109]. Restless legs syndrome symptoms usually appear after the 20th week when associated with pregnancy [2].

The exact incidence of PLMD alone is unknown in adults [2]. However, it is very uncommon in children and is more prevalent after middle age, with approximately 44% of adults 65 years of age or older found to have symptoms of the disorder [2; 129]. It is unclear if the prevalence among older adults differentiates symptoms indicative of idiopathic PLMD and limb movements related to other conditions, but some questions have been raised as to whether PLMD is a true sleep disorder based on the high prevalence in this population [129].

**Risk Factors**

There is a strong heritable risk factor for restless legs syndrome [128; 130]. One study found that more than 70% of pediatric patients with restless legs syndrome had at least one parent with the disorder [109]. As noted, restless legs syndrome is more common in women, but race does not appear to be a factor [2]. Overall, prevalence and incidence have not been well defined [109; 127].

Medical or psychiatric conditions and certain medications have been associated with an increased incidence of restless legs syndrome and/or PLMD. Children with attention deficit hyperactivity disorder are more likely to have both restless legs syndrome and PLMD. Uremia and other metabolic disorders are known to cause periodic limb movements during sleep [2]. Monoamine oxidase inhibitors and tricyclic antidepressants can cause or worsen the disor-

| JOHNS HOPKINS RESTLESS LEGS SYNDROME SEVERITY SCALE | |
|---|---|
| **Timing of Symptoms** | **Score** |
| No symptoms | 0 (never) |
| Symptoms less than daily or almost daily | 0.5 (infrequent) |
| At bedtime and/or during the sleep period.<br>Symptoms may occur within 60 minutes before the usual bedtime or simply at the time of going to bed or during the night after in bed. | 1 (mild) |
| Evening, after 6 p.m.<br>Symptoms may occur anytime between 6 p.m. and the usual bedtime. (The definition of evening may need to be adjusted for patients who routinely have much later bedtimes.) | 2 (moderate) |
| Afternoon, before 6 p.m.<br>Symptoms may start in the afternoon and persist into the evening or night. | 3 (severe) |
| Before noon.<br>Symptoms may start in the morning or they may present virtually all day. There is usually a "protected period" in the mid-morning (8–10 a.m.) with few if any symptoms. | 4 (very severe) |

*Source: Reprinted from Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep Med. 2001;2(3):239-242, with permission from Elsevier.* *Table 5*

der, as can withdrawal from certain drugs, including anticonvulsants, benzodiazepines, barbiturates, and other hypnotic agents. PLMD may be associated with an underlying arousal disorder [128].

### Diagnosis

The history and physical examination should focus on differentiating restless legs syndrome from other conditions with shared features, including akathisia, anxiety disorders, chronic myelopathy, erythromelalgia, leg compartment syndromes, muscular pain fasciculation syndromes, myokymia, and peripheral neuropathy [2]. Subclinical hypopneas can also trigger limb movements. Iron-deficiency anemia, caffeinism, and uremia should also be considered as possible causes of secondary restless legs syndrome. The use of and withdrawal from high-risk medications should also be identified from the medical history. All conditions known to cause the symptoms indicative of the disorder should be ruled out, and serology should be obtained (e.g., cobalamin, creatinine, ferritin, folate, iron, urea) [127; 129; 130]. Additional serology and electrodiagnostic testing may be considered if peripheral neuropathy is suspected. The presence of periodic limb movements during sleep is a strong indication of restless legs syndrome. Several instruments are available to measure restless legs syndrome severity, including the Johns Hopkins Restless Legs Syndrome Severity Scale (***Table 5***) and the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) [131]. The RLS-QLI consists of 17 items that assess the patient's social function, daily function, sleep quality, and emotional well-being, while the Johns Hopkins measure focuses on timing of symptoms [132; 133].

Sleep studies are not typically needed for a diagnosis of restless legs syndrome to be made; however, periodic limb movements during sleep may be confirmed using polysomnography, if necessary [2; 127].

Polysomnographic features of PLMD are recorded using bilateral anterior tibialis EMG. Patterns of movement include repetitive contractions (four or more, with a duration of 0.5 to 5 seconds)—typically a leg jerk, followed by a short interval (milliseconds) and a tonic contraction—spaced apart by 20 to 40 seconds of relaxed muscle tone [2]. Both legs are involved in the majority of patients, but there may be inconsistent and random alternation between the left and right limbs or a unilateral, predominant pattern. The periodic limb movement arousal index measures the number of limb movements associated with EEG arousals per hour. Mild PLMD is defined as 5 to 25 movements per hour, moderate as 25 to 50 per hour, and severe as more than 50 movements per hour or more than 25 movements associated with arousals per hour [129].

**Treatment**

Anticonvulsants, dopamine agonists, tranquilizers, and opioid narcotics are used to manage symptoms of restless legs syndrome, and iron supplements are used when indicated [127; 128]. Dopamine agonists considered effective for restless legs syndrome management include pramipexole and ropinirole, but rotigotine is recommended for long-term therapy [128; 134]. These and other antiparkinsonian drugs are also first-line therapies for PLMD and may improve sleep in patients with both disorders. The anticonvulsants gabapentin and pregabalin reduce movement symptoms and neuropathic pain in patients with either restless legs syndrome or PLMD and may also help to improve sleep; however, use of these medications for restless legs syndrome and PLMD is off-label [57; 128]. Gabapentin enacarbil is on-label and is preferred over gabapentin for long-term treatment [57; 134]. Other treatments for these sleep disorders include stress management, muscle relaxation exercises, and sleep hygiene.

The initial dosage of pramipexole (immediate-release) is 0.125 mg once daily, two to three hours before bedtime, but higher doses (up to 0.5 mg) are typically required in order to be effective [57]. The maximum recommended dose is 0.5 mg, but doses up to 2 mg daily are occasionally used. The most frequent side effects are nausea (11% to 27%), particularly early in treatment, and headache (16%) [57]. There is no evidence that doses higher than 0.5 mg/day offer benefit [135].

The initial dose of ropinirole (immediate-release) is 0.25 mg taken one to three hours before bedtime; the dose may be increased to 0.5 mg after two days, to 1 mg after one week, and to a maximum dose of 4 mg at week 7. Common adverse effects include dizziness (6% to 40%), fatigue (8% to 11%), nausea (40% to 60%), somnolence (11% to 40%), syncope (1% to 12%), and viral infection (11%) [57].

The American Academy of Sleep Medicine has identified gabapentin and pregabalin as the agents with the highest level of evidence supporting their use in the treatment of adults with restless legs syndrome.

(https://jcsm.aasm.org/doi/10.5664/jcsm.11390. Last accessed December 16, 2024.)

**Strength of Recommendation/Level of Evidence**: Strong recommendation, moderate certainty of evidence

The rotigotine (transdermal patch) initial dose is 1 mg/24 hours (one patch per day). The daily dose may be increased by 1 mg/24 hours each week, to a maximum daily dose of 3 mg/24 hours [57]. Dose-related application site reactions are common (21% to 46%), as are gastrointestinal complications such as nausea (15% to 48%) and vomiting (2% to 20%), and CNS reactions (e.g., somnolence, dizziness, headache, fatigue, orthostatic hypotension, hallucinations) [57]. Therefore, an extended low-dose trial is recommended.

Higher doses of gabapentin (2,000–2,400 mg daily) have been found to be significantly more effective than placebo in reducing moderate-to-severe restless legs syndrome symptoms, but higher doses are also associated with a high prevalence of adverse effects (e.g., dizziness, fatigue, nausea, pain, weakness) [57]. The recommended initial dose for restless legs syndrome treatment (off-label) is 300 mg taken two hours before bedtime; the dose may be titrated every two weeks, until desired response is achieved, to a maximum dose of 1,800 mg [57]. (Dosages of up to 3,600 mg have been tolerated in short-term studies but are not recommended.)

Gabapentin enacarbil is FDA-approved for the treatment of restless legs syndrome and is preferred over gabapentin due to longer duration of action and improved absorption [57; 134; 137]. The dosage is 300-600 mg once daily at approximately 5 p.m. Worsening side effects are seen at higher doses, and no benefit is reported at a dose of 1,200 mg compared with 600 mg [57]. Adverse effects (at a 600-mg daily dose) include dizziness (13% to 17%), headache (10% to 12%), and somnolence (20%), and a low rate of gastrointestinal effects are also observed (e.g., nausea, 6% to 8%) [57]. Pooled analysis of long-term use of gabapentin and other antiepileptic drugs has validated concerns regarding suicidal ideation and behavior (0.43%) compared with placebo (0.24%) [57]. Human data regarding pancreatic cancer risk have yet to be compiled, although gabapentin is associated with pancreatic adenocarcinoma in rats [57; 137].

Multiple studies have shown that pregabalin is effective for managing sensory and motor symptoms of restless legs syndrome and has a low rate of mild adverse effects across a wide dosage range [138; 139]. A reduction of periodic limb movements and sleep architecture improvements (e.g., increase in slow-wave sleep, decrease in waking after sleep onset and during sleep stages 1 and 2) were noted. In one study, the mean effective dose for pregabalin was approximately 350 mg/day, but in another study, a dose of 125 mg/day was shown to be effective in 90% of participants [138; 139]. Pregabalin is usually taken in divided doses, either two or three times a day [57]. Dizziness (3% to 45%) and somnolence (17% to 26%) are the most frequent adverse effects [57; 138].

### *Lifestyle Modifications and Alternative Therapies*

Stress reduction, muscle relaxation techniques, and physical activity are important components of a restless legs syndrome management strategy, along with improved nutrition, proper sleep hygiene, and elimination of caffeine and alcohol intake [128; 129; 130; 131]. Supplementation with specific vitamins and minerals known to support the nervous system and improve blood circulation (e.g., vitamins B12, C, D, and E; glucosamine; magnesium; zinc) may be considered for patients with inadequate nutritional intake, but little research exists apart from small studies showing some degree of symptom reduction with supplementation with vitamins B and E [131]. Other alternative therapies with little or no scientific support include acupuncture, meditation, and prayer.

Moderate aerobic exercise and lower-body resistance training are recommended to both assist in the relief of psychological stress and lessen the severity of symptoms [128]. Endorphin release, dopamine production, and increased blood flow to leg muscles are believed to mediate symptoms [131]. Massage, warm baths, and heating pads may also be used to relieve and/or prevent restless legs syndrome symptoms, though there is a lack of strong efficacy data for these therapies [130]. Case studies have shown a positive effect with massage (and a return of symptoms after cessation of massage therapy regimens), but the mechanisms involved are unclear [131]. Theories include improved blood circulation, dopamine release, counterstimulation of the cerebral cortex, and modulated thalamic neural activity as a response to tactile and temperature stimulus. Pulsed pneumatic compression devices have also been shown to reduce symptom severity; the proposed beneficial mechanisms are similar to

those of massage [131]. Near-infrared light therapy has also successfully reduced restless legs syndrome symptom severity in small-scale studies [140].

There is a strong placebo effect in restless legs syndrome therapy [131]. A 2008 meta-analysis of 36 clinical trials found that one-third of patients had a significant improvement while receiving placebo medications [141]. In 24 of the trials, 40% of participants had a placebo response. However, this level of response was based on a reduction in the International Restless Legs Severity Scale score alone, and the placebo response was only moderate for other measures (e.g., daytime functioning, other restless legs syndrome measures). The placebo effect was found to be small for PLMD therapy [141].

In 2014, the FDA cleared the first device to improve sleep quality in patients with restless legs syndrome [142]. The device, marketed as Relaxis, consists of a vibrating pad that provides counterstimulation to a patient's legs as he or she sleeps. The manufacturer cautions that this device should not be used on patients who have had deep venous thrombosis in either leg in the six months prior to the initiation of therapy.

## DIAGNOSING AND TREATING SLEEP DISORDERS WITH THE HELP OF AN INTERPRETER

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such a vital aspect of the treatment and management of sleep disorders, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures are being provided, the use of an interpreter should be considered.

## INTERPROFESSIONAL COLLABORATION IN THE DIAGNOSIS AND TREATMENT OF SLEEP DISORDERS

Collaboration between generalists and sleep specialists has been recommended to alleviate the gaps in primary care providers' knowledge of sleep disorders [150; 151]. However, true interprofessional collaboration and care delivery can be difficult. In one study, specialists reported that while some primary care physicians have been receptive to sleep education in the past, they were reluctant to take the responsibility for interpreting polysomnography results and for treatment [152]. Further, healthcare systems and insurance providers may present barriers to interprofessional collaborative care in cases of sleep disorders. For example, dental professional are often essential to the identification of obstructive sleep apnea in adults. Increasing knowledge of each team members role, providing opportunities for collaboration and referral, and engaging in educational activities to improve knowledge of and adherence to clinical guidelines can all help support interprofessional team care.

## CONCLUSION

Consistent and refreshing sleep is vital to health and an overall sense of wellness. However, nearly 25% of the U.S. population is troubled by a sleep disorder, many of which remain undiagnosed or undertreated, leading to a sleep deficit that can be difficult or impossible to repay. While most forms of disturbed sleep are not life-threatening, they can cause considerable distress, including accidental injury, depression, fatigue, and substance abuse. Most patients with a sleep disorder initially present to their primary care provider or other non-specialist, and appropriate identification and treatment or referral are important in this setting. This is especially true for the handful of sleep disorders that cause the majority of morbidity and mortality, including obstructive sleep apnea, narcolepsy, and insomnia. Increased understanding and adherence to best practices can improve patients' quality of life and help prevent associated complications.

**Implicit Bias in Health Care**

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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