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avoid making a diagnosis of “frontal lobe syndrome” in a patient with no evidence of frontal cortex disease, it is advisable to use the diag nostic term frontal network syndrome, with the understanding that the responsible lesions can lie anywhere within this distributed network. A patient with frontal lobe disease raises potential dilemmas in differ ential diagnosis, especially if the cause is neurodegenerative: the abulia and blandness may be misinterpreted as depression, and the disinhibi tion as idiopathic mania or acting out. CARING FOR PATIENTS WITH DEFICITS

OF HIGHER CEREBRAL FUNCTION Spontaneous improvement of cognitive deficits following stroke or trauma is common. It is most rapid in the first few weeks but may continue for up to 2 years, especially in young individuals with single brain lesions. Some of the initial deficits in such cases appear to arise from remote dysfunction (diaschisis) in brain regions that are inter connected with the site of initial injury. Improvement in these patients may reflect, at least in part, a normalization of the remote dysfunction. Other mechanisms may involve functional reorganization in surviving neurons adjacent to the injury or the compensatory use of homologous structures. In contrast, neurodegenerative diseases show a progression of impairment but at rates that vary greatly from patient to patient. Pharmacologic and Nonpharmacologic Interventions Some of the deficits described in this chapter are so complex that they may bewilder not only the patient and family but also the physician. The care of patients with such deficits requires a careful evaluation of the history, cognitive test results, and diagnostic procedures. Each piece of information needs to be interpreted cautiously and placed in context. A complaint of “poor memory,” for example, may reflect an anomia; poor scores on a learning task may reflect a weakness of attention rather than explicit memory; a report of depression or indifference may reflect impaired prosody rather than a change in mood or empa thy; jocularity may arise from poor insight rather than good mood. Treatment plans should encompass two levels: a symptomatic level that can be addressed by pharmacologic or nonpharmacologic means and a disease level that needs to be addressed through pharmacologic or molecular interventions. Although there are few well-controlled stud ies, several nonpharmacologic interventions have been used to treat higher cortical deficits. These include speech therapy for aphasias, behavioral modification for compartmental disorders, and cogni tive training for visuospatial disorientation and amnestic syndromes. More practical interventions, usually delivered through occupational therapy, aim to improve daily living activities through assistive devices and modifications of the home environment. Determining driving competence is challenging, especially in the early stages of dementing diseases. An on-the-road driving test and reports from family mem bers may help time decisions related to this very important activity. In neurodegenerative conditions such as PPA, transcranial magnetic (or direct current) stimulation has had mixed success in eliciting symp tomatic improvement. The goal is to activate remaining neurons at sites of atrophy or in unaffected regions of the contralateral

hemisphere. Depression and sleep disorders can intensify the cognitive disorders and should be treated with appropriate modalities. If neuroleptics become necessary for the control of agitation, atypical neuroleptics are preferable because of their lower extrapyramidal side effects. Treatment with neuroleptics in elderly patients with dementia requires weighing the potential benefits against the potentially serious side effects. This is especially relevant to the case of patients with Lewy body dementia, who can be unusually sensitive to side effects. As in all other branches of medicine, a crucial step in patient care is to identify the underlying cause of the impairment. This is easily done in cases of CVA, head trauma, or encephalitis but becomes particularly challenging in neurodegenerations because the same progressive clinical syndrome can be caused by one of several neuropathologic entities. The advent of imaging, blood, and cerebrospinal fluid biomarkers now makes it possible to address this question with reasonable success and to make specific diagnoses of AD, LBD, CJD, and FTLD. A specific etiologic diagnosis allows the physician to recommend medications or clinical

trials that are the most appropriate for the underlying disease process. A clinical assessment that identifies the principal domain of behavioral and cognitive impairment followed by the judicious use of biomarker information to surmise the nature of the underlying disease allows a personalized approach to patients with higher cognitive impairment.

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Charles A. Czeisler

Sleep Disorders Disturbed sleep is one of the most common health complaints that physicians encounter. More than one-half of adults in the United States experience at least intermittent sleep disturbance, and only 30% of adult Americans report consistently obtaining a sufficient amount of sleep. The National Academy of Medicine has estimated that 50–70 million Americans suffer from a chronic disorder of sleep and wakefulness, which can adversely affect daytime functioning as well as physical and mental health. A high prevalence of sleep disorders across all cultures is also now increasingly recognized, and these problems are expected to further increase in the years ahead as the global population ages. Over the past 40 years, the field of sleep medicine has emerged as a distinct specialty in response to the impact of sleep disorders and sleep deficiency on overall health. Nonetheless, >80% of patients with sleep disorders remain undiagnosed and untreated—costing the U.S. economy >$400 billion annually in increased health care costs, lost

productivity, accidents, and injuries, and leading to the development of workplace-based sleep health education and sleep disorders screening programs designed to address this unmet medical need. PHYSIOLOGY OF SLEEP AND WAKEFULNESS Most adults need 7–9 h of sleep per night to promote optimal health, although the timing, duration, and internal structure of sleep vary among individuals. In the United States, adults tend to have one consolidated sleep episode each night, although in some cultures, sleep may be divided into a mid-afternoon nap and a shortened night sleep. This pattern changes considerably over the life span, as infants and young children sleep considerably more than older people, while

individuals >70 years of age sleep on average about an hour less than young adults.

The stages of human sleep are defined on the basis of characteristic patterns in the electroencephalogram (EEG), the electrooculogram (EOG—a measure of eye-movement activity), and the surface elec tromyogram (EMG) measured on the chin and legs. The continuous recording of these electrophysiologic parameters to define sleep and wakefulness is termed polysomnography. Polysomnographic profiles define two basic states of sleep: (1) rapid eye movement (REM) sleep and (2) non–rapid eye movement (NREM) sleep. NREM sleep is further subdivided into three stages: N1, N2, and N3, characterized by an increasing threshold for arousal and slowing of the cortical EEG. REM sleep is distinguished by a low-amplitude, mixed-frequency EEG, similar to NREM stage N1 sleep, and an EOG pattern of REMs that tend to occur in flurries or bursts. EMG activ ity is absent in nearly all skeletal muscles except those involved in respiration, reflecting the brainstem-mediated muscle paralysis that is characteristic of REM sleep. PART 2 Cardinal Manifestations and Presentation of Diseases ■ ■ORGANIZATION OF HUMAN SLEEP Normal nocturnal sleep in adults displays a consistent organization from night to night (Fig. 33-1). After sleep onset, sleep usually pro gresses through NREM stages N1–N3 sleep within 45–60 min. NREM stage N3 sleep (also known as slow-wave sleep) predominates in the first third of the night and comprises 15–25% of total nocturnal sleep time in young adults. Sleep deprivation increases the rapidity of sleep onset and both the intensity and amount of slow-wave sleep. The first REM sleep episode usually occurs in the second hour of sleep. NREM and REM sleep alternate through the night with an aver age period of 60–160 min (the “ultradian” sleep cycle). Overall, in a healthy young adult, REM sleep constitutes 20–25% of total sleep, and NREM stages N1 and N2 constitute 50–60%. Age has a profound impact on sleep state organization (Fig. 33-1). N3 sleep is most intense and prominent during childhood, decreasing with puberty and across the second and third decades of life. In older adults, N3 sleep may be completely absent, and the remaining NREM sleep typically becomes more fragmented, with frequent awakenings from NREM sleep. Older people spend more time awake during their sleep episode, mainly due to more awakenings, rather than a decreased ability to fall back asleep. While REM sleep may account for 50% of total sleep time in infancy, the percentage falls off sharply over the first postnatal year as a mature REM-NREM cycle develops; in young adults, REM sleep occupies about 25% of total sleep time. Sleep deprivation degrades cognitive performance, particularly on tests that require continual vigilance. Young adults are particularly sus ceptible to slowed reaction times and difficulty maintaining vigilance during sleep deprivation, which may in part account for the large num ber of motor vehicle accidents in this age group late at night. Age 23 N2 N1 REM Awake N3 Age 68 N3 N2 N1 REM Awake 02.00 04.00 06.00 08.00 Clock time 00.00 FIGURE 33-1 Wake-sleep architecture. Alternating stages of wakefulness, the three stages of non–rapid eye movement sleep (N1–N3), and rapid eye movement (REM) sleep (solid bars) occur over the course of the night for representative young and older adult

men. Characteristic features of sleep in older people include reduction of N3 slow-wave sleep, frequent spontaneous awakenings, early sleep onset, and early morning awakening.

After sleep deprivation, NREM sleep generally recovers first, fol lowed by REM sleep. However, because REM sleep tends to be most prominent in the second half of the night, sleep truncation (e.g., by an alarm clock) results in selective REM sleep deprivation. This may increase REM sleep pressure to the point where the first REM sleep may occur much earlier in the nightly sleep episode. To avoid these influences, it is important that the patient have sufficient sleep oppor tunity (at least 8 h per night) for several nights prior to a diagnostic polysomnogram. Beyond impaired cognition, chronic sleep deficiency is associated with glucose intolerance that may contribute to the development of diabetes, obesity, and the metabolic syndrome, as well as impaired immune responses, accelerated atherosclerosis, and increased risk of cardiac disease, cognitive impairment, Alzheimer's disease, and stroke. For these reasons, the National Academy of Medicine declared sleep deficiency and sleep disorders "an unmet public health problem." ■ ■WAKE AND SLEEP ARE REGULATED

BY BRAIN CIRCUITS Two principal neural systems govern the expression of sleep and wake fulness. The ascending arousal system, illustrated in green in Fig. 33-2, consists of clusters of nerve cells extending from the upper pons to the hypothalamus and basal forebrain that activate the cerebral cortex, thalamus (which is necessary to relay sensory information to the cor tex), and other forebrain regions. The ascending arousal neurons use monoamines (norepinephrine, dopamine, serotonin, and histamine), glutamate, or acetylcholine as neurotransmitters to activate their tar get neurons. Some basal forebrain neurons use γ-aminobutyric acid (GABA) to inhibit cortical inhibitory interneurons, thus promoting arousal. Additional wake-promoting neurons in the hypothalamus use the peptide neurotransmitter orexin (also known as hypocretin, shown in Fig. 33-2 in blue) to reinforce activity in the other arousal-promoting cell groups. Damage to the arousal system at the level of the rostral pons and lower midbrain causes coma, indicating that the ascending arousal influence from this level is critical in maintaining wakefulness. Injury to the arousal system in the midbrain or hypothalamus causes pro found sleepiness. Specific loss of the orexin neurons produces the sleep disorder narcolepsy (see below). Isolated damage to the thalamus causes loss of the content of wakefulness, known as a persistent vegeta tive state, but wake-sleep cycles are largely preserved. The arousal system is turned off during sleep by inhibitory inputs from cell groups in the sleep-promoting system, shown in Fig. 33-2 in red. These neurons in the preoptic area and pons use GABA to inhibit the arousal system. Additional neurons in the lateral hypothalamus containing the peptide melanin-concentrating hormone promote REM sleep. Many sleep-promoting neurons are themselves inhibited by inputs from the arousal system. This mutual inhibition between the arousal- and sleep-promoting systems forms a neural circuit akin to what electrical engineers call a "flip-flop switch." A switch of this type tends to promote rapid transitions between the on (wake) and off (sleep) states, while avoiding intermediate states. The relatively rapid transitions between waking and sleeping states, as seen in the EEG of humans and animals, is consistent with this model. Neurons in the ventrolateral preoptic nucleus, one of the key sleep-promoting sites, are lost during normal human aging, correlating with reduced ability to maintain sleep (sleep fragmentation). The ventrolateral preoptic neurons are also injured in Alzheimer's disease, which may in part account for the poor sleep quality in those patients. Transitions between NREM and REM sleep appear to be governed by a similar switch in the brainstem. GABAergic REM-Off neurons have been identified in the lower mid brain that inhibit REM-On neurons in the upper

pons. The REM-On group contains both GABAergic neurons that inhibit the REM-Off group (thus satisfying the conditions for a REM sleep flip-flop switch) as well as glutamatergic neurons that project widely in the central nervous system

Inhibitors of arousal systems: H1 antagonists Alpha-2 agonists Muscarinic antagonists Orexin antagonists Thalamus Hypothalamus Ascending arousal system GABAergic arousal inhibiting system Potentiators of GABA inhibition: Benzodiazepines Barbiturates Ethanol Chloral hydrate Orexin (hypocretin) system FIGURE 33-2 Relationship of drugs for insomnia with wake-sleep systems. The arousal system in the brain (green) includes monoaminergic, glutamatergic, and cholinergic neurons in the brainstem that activate neurons in the hypothalamus, thalamus, basal forebrain, and cerebral cortex. Orexin neurons (blue) in the hypothalamus, which are lost in narcolepsy, reinforce and stabilize arousal by activating other components of the arousal system. The sleep-promoting system (red) consists of GABAergic neurons in the preoptic area and brainstem that inhibit the components of the arousal system, thus allowing sleep to occur. Drugs used to treat insomnia include those that block the effects of arousal system neurotransmitters (green and blue) and those that enhance the effects of γ-aminobutyric acid (GABA) produced by the sleep system (red). to cause the key phenomena associated with REM sleep. REM-On neurons that project to the medulla and spinal cord activate inhibitory (GABA and glycine-containing) interneurons, which in turn hyper polarize the motor neurons, producing the paralysis of REM sleep. REM-On neurons that project to the forebrain may be important in producing dreams. The REM sleep switch receives cholinergic input, which favors transitions to REM sleep, and monoaminergic (norepinephrine and serotonin) input that prevents REM sleep. As a result, drugs that increase monoamine tone (e.g., serotonin or norepinephrine reuptake inhibitors) tend to reduce the amount of REM sleep. Damage to the neurons that promote REM sleep paralysis can produce REM sleep behavior disorder, a condition in which patients act out their dreams (see below). ■ ■SLEEP-WAKE CYCLES ARE DRIVEN BY HOMEOSTATIC, ALLOSTATIC, AND

CIRCADIAN INPUTS The gradual increase in sleep drive with prolonged wakefulness, fol lowed by deeper slow-wave sleep and prolonged sleep episodes, dem onstrates that there is a homeostatic mechanism that regulates sleep. The neurochemistry of sleep homeostasis is only partially understood, but with prolonged wakefulness, adenosine levels rise in parts of the brain. Adenosine may act through A1 receptors to directly inhibit many arousal-promoting brain regions. In addition, adenosine pro motes sleep through A2a receptors; blockade of these receptors by caffeine is one of the chief ways in which people fight sleepiness. Other humoral factors, such as prostaglandin D2, have also been implicated in this process. Both adenosine and prostaglandin D2 activate the sleeppromoting neurons in the ventrolateral preoptic nucleus. Allostasis is the physiologic response to a challenge such as physical danger or psychological threat that cannot be managed by homeostatic mechanisms. These stress responses can severely impact the need for and ability to sleep. For example, insomnia is very common in patients with anxiety and other psychiatric disorders. Intermittent stress-induced insomnia is even more common, affecting most people at some time

in their lives. Positron emission tomography (PET) studies in patients with chronic insomnia show hyperactivation of components of the ascending arousal system, as well as their limbic system targets in the forebrain (e.g., cingulate cortex and amygdala). The limbic areas are not only targets for the arousal system, but they also send excitatory outputs back to the arousal system, which

contributes to a vicious cycle of anxiety about insomnia that makes it more difficult to sleep. Approaches to treating insomnia may employ drugs that either inhibit the output of the ascending arousal system (green and blue in Fig. 33-2) or potentiate the output of the sleep-promoting system (red in Fig. 33-2). However, behavioral approaches (cognitive behavioral therapy [CBT] and sleep hygiene) that may reduce forebrain limbic activity at bedtime are often the best long-term treatment.

Sleep Disorders CHAPTER 33 Wakefulness and sleep are also regulated by a strong circadian tim ing signal, driven by the suprachiasmatic nuclei (SCN) of the hypo thalamus, as described below. The SCN sends outputs to key sites in the hypothalamus, which impose 24-h rhythms on a wide range of behaviors and body systems, including the wake-sleep cycle. ■ ■PHYSIOLOGY OF CIRCADIAN RHYTHMICITY The wake-sleep cycle is the most evident of many 24-h rhythms in humans. Prominent daily variations also occur in endocrine, thermo regulatory, cardiac, pulmonary, renal, immune, gastrointestinal, and neurobehavioral functions. In evaluating daily rhythms in humans, it is important to distinguish between diurnal components passively evoked by periodic environmental or behavioral changes (e.g., the increase in blood pressure and heart rate that occurs upon assumption of the upright posture) and circadian rhythms actively driven by an endogenous oscillatory process (e.g., the circadian variations in adrenal cortisol and pineal melatonin secretion that persist across a variety of environmental and behavioral conditions). At the cellular level, endogenous circadian rhythmicity is driven by self-sustaining molecular genetic feedback loops. These clock gene feedback loops of approximately 24 h duration are found in most if not all cells in the body and regulate diverse physiologic processes. However, when cells in most tissues are placed in isolation, they soon fall out of synchrony with each other and can no longer produce useful 24-h rhythms of tissue function. The only tissue that maintains this rhythm in isolation is the SCN, whose neurons are interconnected with one another in such a way as to produce a near-24-h synchronous rhythm of neural activity even in prolonged slice culture. SCN neurons are located just above the optic chiasm in the hypothalamus, from which they receive visual input to synchronize them with the external world, and they have outputs to transmit circadian timing signals to the rest of the body. Bilateral destruction of the SCN results in a loss of most endogenous circadian rhythms including wake-sleep behavior and rhythms in endocrine and metabolic systems. The genetically determined period of this endogenous neural oscillator, which aver ages ~24.15 h in humans, is normally synchronized to the 24-h period of the environmental light-dark cycle through direct input to the SCN from intrinsically photosensitive ganglion cells in the retina. Humans are exquisitely sensitive to the resetting effects of light, particularly the shorter wavelengths (~460–500 nm) in the blue part of the visible spec trum. Small differences in circadian period contribute to variations in diurnal preference. For example, people with short circadian cycles (e.g., 23.5 h) due to mutations of circadian clock genes prefer an early bedtime and wake up in the early morning hours (known as advanced sleep phase disorder). The timing and internal architecture of sleep are directly coupled to the output of the endogenous circadian pacemaker. Paradoxically, the endogenous circadian rhythm for wake propensity peaks just before the habitual bedtime, whereas that of sleep propensity peaks near the habitual wake time. These rhythms are thus timed to oppose the rise of homeostatic sleep tendency throughout the usual waking day and the decline of sleep propensity during the habitual sleep episode, respectively, thus promoting consolidated sleep and wakefulness. Mis alignment of the endogenous circadian pacemaker with the desired wake-sleep cycle can, therefore, induce insomnia (especially diffi culty initiating sleep or waking earlier than desired in the morning),

decrease alertness, and impair performance, posing health problems for night-shift workers and airline travelers. In addition, mounting evidence indicates that sleep regularity may be as important as sleep duration in terms of physical and mental health outcomes.

Participants awakened from REM sleep recall vivid dream imagery

> 80% of the time, especially later in the night. Less vivid imagery may also be reported after NREM sleep interruptions. Certain disorders may occur during specific sleep stages and are described below under “Parasomnias.” These include sleepwalking, night terrors, and enuresis (bed wetting), which occur most commonly in children during deep (N3) NREM sleep. In contrast, REM sleep behavior disorder occurs mainly among older people who fail to main tain full paralysis during REM sleep, and often call out, thrash around, or even act out fragments of dreams. PART 2 Cardinal Manifestations and Presentation of Diseases All major physiologic systems are influenced by sleep. Blood pres sure and heart rate decrease during NREM sleep, particularly during N3 sleep. During REM sleep, bursts of eye movements are associated with large variations in both blood pressure and heart rate mediated by the autonomic nervous system. Cardiac dysrhythmias may occur selec tively during REM sleep. Respiratory function also changes. In com parison to relaxed wakefulness, respiratory rate becomes slower and more regular during NREM sleep (especially N3 sleep) and becomes irregular during bursts of eye movements in REM sleep. Decreases in minute ventilation during sleep are out of proportion to the decrease in metabolic rate, resulting in a slightly higher PCO2. Within the brain itself, neurotransmission is supported by ion gra dients across the cell membranes of neurons and astrocytes. These ion flows are accompanied by increases in intracellular volume, so that during wake there is very little extracellular space in the brain. During sleep, intracellular volume is reduced, resulting in increased extracel lular space, which has higher calcium and lower potassium concentra tions, supporting hyperpolarization and reduced firing of neurons. This expansion of the extracellular space during sleep increases dif fusion of substances that accumulate extracellularly, like β-amyloid peptide, enhancing their clearance from the brain via cerebrospinal fluid (CSF) flow. Recent evidence suggests that lack of adequate sleep may contribute to extracellular accumulation of β-amyloid peptide, a key step in the pathogenesis of Alzheimer’s disease. Endocrine function also varies with sleep. N3 sleep is associated with secretion of growth hormone in men, while sleep in general is associated with augmented secretion of prolactin in both men and women. Sleep has a complex effect on the secretion of luteinizing hormone (LH): during puberty, sleep is associated with increased LH secretion, whereas sleep in postpubertal women inhibits LH secretion in the early follicular phase of the menstrual cycle. Sleep onset (and probably N3 sleep) is associated with inhibition of thyroid-stimulating hormone and of the adrenocorticotropic hormone–cortisol axis, an effect that is superimposed on the prominent

> circadian rhythms in the two systems. The hormone melatonin is secreted from the pineal gland pre dominantly at night in both day- and night-active species, under the control of the SCN. Melatonin secretion does not require sleep, but melatonin secretion is inhibited by ambient light, an effect mediated by the neural connection from the retina to the SCN and then on to the pineal gland via the sympathetic nervous system. In humans, sleep efficiency is highest when sleep coincides with endogenous melatonin secretion. When endogenous melatonin levels are low, such as during the biological day or at the desired bedtime in people with delayed sleep-wake phase disorder (DSWPD), administration of exogenous melatonin can hasten sleep onset and increase sleep efficiency, but it does not increase sleep efficiency if administered when endogenous melatonin levels are elevated. This may explain why melatonin is often ineffective in the treatment of patients with primary insomnia. On the other hand, patients with sympathetic denervation of the pineal gland, such as occurs in cervical spinal cord injury or in patients with Parkin son's disease, often have low melatonin levels, and administration of melatonin (3 mg 30 min before bedtime) may help them sleep. Sleep is accompanied by alterations of thermoregulatory func tion. Warming the skin is associated with an increase in the firing of

warm-responsive neurons in the preoptic area, which cause a fall in body temperature and promote onset of NREM sleep. REM sleep is associated with reduced thermoregulatory responsiveness. DISORDERS OF SLEEP AND WAKEFULNESS APPROACH TO THE PATIENT Sleep Disorders Patients may seek help from a physician because of: (1) sleepiness or tiredness during the day; (2) difficulty initiating or maintaining sleep at night (insomnia); or (3) unusual behaviors during sleep itself (parasomnias). Obtaining a careful history is essential. In particular, the dura tion, severity, and consistency of the symptoms are important, along with the patient's estimate of the consequences of the sleep disorder on waking function. Information from a bed partner or family member is often helpful because some patients may be unaware of symptoms such as heavy snoring or may underreport symptoms such as falling asleep at work or while driving. Physicians should inquire about when the patient typically goes to bed, when they fall asleep and wake up, whether they awaken during sleep, whether they feel rested in the morning, and whether they nap during the day. Depending on the primary complaint, it may be useful to ask about snoring, witnessed apneas, restless sensations in the legs, movements during sleep, depression, anxiety, and behaviors around the sleep episode. The physical examination may provide evidence of a small airway, large tonsils, or a neurologic or medical disorder that contributes to the main complaint. It is important to remember that, rarely, seizures may occur exclusively during sleep, mimicking a primary sleep disorder; such sleep-related seizures typically occur during episodes of NREM sleep and may take the form of generalized tonic-clonic movements (sometimes with urinary incontinence or tongue biting) or stereo typed movements in partial complex epilepsy (Chap. 436). It is often helpful for the patient to complete a daily sleep log for 1–2 weeks to define the timing and amounts of sleep. When relevant, the log can also include information on levels of alert ness, work times, and drug and alcohol use, including caffeine and hypnotics. Polysomnography is necessary for the diagnosis of several disor ders such as sleep apnea, narcolepsy, and periodic

limb movement disorder (PLMD). A conventional polysomnogram performed in a clinical sleep laboratory allows measurement of sleep stages, respiratory effort and airflow, oxygen saturation, limb movements, heart rhythm, and additional parameters. A home sleep test usually focuses on just respiratory measures and is helpful in patients with a moderate to high likelihood of having obstructive sleep apnea. The multiple sleep latency test (MSLT) is used to measure a patient's propensity to sleep during the day and can provide crucial evidence for diagnosing narcolepsy and some other causes of sleepiness. The maintenance of wakefulness test is used to measure a patient's ability to sustain wakefulness during the daytime and can provide important evidence for evaluating the efficacy of therapies for improving sleepiness in conditions such as narcolepsy and obstruc tive sleep apnea. ■ ■EVALUATION OF DAYTIME SLEEPINESS Up to 25% of the adult population has persistent daytime sleepiness that impairs an individual's ability to perform optimally in school, at work, while driving, and in other conditions that require alertness. Sleepy students often have trouble staying alert and performing well in school, and sleepy adults struggle to stay awake and focused on their work. More than half of Americans have fallen asleep while driving. An estimated 1.2 million motor vehicle crashes per year are due to drowsy drivers, causing about 20% of all serious crash injuries and deaths. One need not fall asleep to have a motor vehicle crash, as the inatten tion and slowed responses of drowsy drivers are major contributors.

Twenty-four hours of continuous wakefulness impairs reaction time as much as a blood alcohol concentration of 0.10 g/dL (which is legally drunk in all 50 states). Identifying and quantifying sleepiness can be challenging. First, patients may describe themselves as "sleepy," "fatigued," or "tired," and the meanings of these words may differ between patients. For clinical purposes, it is best to use the term "sleepiness" to describe a propen sity to fall asleep, whereas "fatigue" is best used to describe a feeling of low physical or mental energy but without a tendency to actually sleep. Sleepiness is usually most evident when the patient is sedentary, whereas fatigue may interfere with more active pursuits. Sleepiness generally occurs with disorders that reduce the quality or quantity of sleep or that interfere with the neural mechanisms of arousal, whereas fatigue is more common in inflammatory disorders such as cancer, multiple sclerosis (Chap. 455), post-COVID syndrome (Chap. 205), fibromyalgia (Chap. 385), myalgic encephalomyelitis/chronic fatigue syndrome (Chap. 461), or endocrine deficiencies such as hypothyroid ism (Chap. 395) or Addison's disease (Chap. 398). Second, sleepiness can affect judgment in a manner analogous to ethanol, such that patients may have limited insight into the condition and the extent of their functional impairment. Finally, patients may be reluctant to admit that sleepiness is a problem because they may have become unfamiliar with feeling fully alert, and because sleepiness is sometimes viewed pejoratively as reflecting poor motivation or bad sleep habits. Table 33-1 outlines the diagnostic and therapeutic approach to the patient with a complaint of excessive daytime sleepiness. To determine the extent and impact of sleepiness on daytime func tion, it is helpful to ask patients about the occurrence of sleepiness and sleep episodes during normal waking hours, both intentional and unintentional. Specific areas to be addressed include the occurrence of inadvertent sleep episodes while driving or in other safety-related settings, sleepiness while at work or school (and its impact on perfor mance), and the effect of sleepiness on social and family life. Standard ized questionnaires such as the Epworth Sleepiness Scale are often used clinically to measure sleepiness. Eliciting a history of daytime sleepiness is usually adequate, but objective quantification is sometimes necessary. The MSLT measures a patient's propensity to sleep under quiet conditions. An overnight poly somnogram should precede the MSLT to establish that the patient has had an adequate amount of good-quality nighttime sleep. The MSLT consists of

five 20-min nap opportunities every 2 h across the day. The patient is instructed to try to fall asleep, and the major endpoints are the average latency to sleep and the occurrence of REM sleep during the naps. An average sleep latency across the naps of <8 min is con sidered objective evidence of excessive daytime sleepiness. REM sleep normally occurs only during nighttime sleep, and the occurrence of REM sleep in two or more of the MSLT daytime naps provides support for the diagnosis of narcolepsy. TABLE 33-1 Evaluation of the Patient with Excessive Daytime Sleepiness FINDINGS ON HISTORY AND PHYSICAL EXAMINATION DIAGNOSTIC EVALUATION DIAGNOSIS THERAPY Difficulty waking in the morning, rebound sleep on weekends and vacations with improvement in sleepiness Sleep log Insufficient sleep Sleep education and behavioral modification to increase amount of sleep Obesity, snoring, hypertension Polysomnogram or home sleep test Cataplexy, hypnagogic hallucinations, sleep paralysis Polysomnogram and multiple sleep latency test Restless legs, kicking movements during sleep Assessment for predisposing medical conditions (e.g., iron deficiency or renal failure) Sedating medications, stimulant withdrawal, head trauma, systemic inflammation, Parkinson’s disease and other neurodegenerative disorders, hypothyroidism, encephalopathy Thorough medical history and examination including detailed neurologic examination

For the safety of the individual and the general public, physicians have a responsibility to help manage issues around driving in patients with sleepiness. Legal reporting requirements vary between states and countries, but at a minimum, physicians should inform sleepy patients about their increased risk of having an accident and advise such patients not to drive a motor vehicle until their sleepiness has been treated effectively. This discussion is especially important for com mercial drivers, and it should be documented in the patient’s medical record.

Sleep Disorders CHAPTER 33 ■ ■INSUFFICIENT SLEEP Insufficient sleep is probably the most common cause of excessive daytime sleepiness. The average adult needs 7.5–8 h of sleep, but on weeknights, the average U.S. adult obtains only 6.75 h of sleep. Only 30% of the U.S. adult population reports consistently obtaining suffi cient sleep. Insufficient sleep is especially common among shift work ers, individuals working multiple jobs, people in lower socioeconomic groups, and historically minority populations. Most teenagers need ≥9 h of sleep, but many fail to get enough sleep because of circadian phase delay, plus social pressures to stay up late coupled with early school start times. Late evening light exposure, homework, television view ing, video-gaming, social media, texting, and smartphone use often delay bedtimes, despite the fixed early wake times required for work or school. As is typical with any disorder that causes sleepiness, indi viduals with chronically insufficient sleep may feel inattentive, irritable, unmotivated, and depressed, and have difficulty with school, work, and driving. Individuals differ in their optimal amount of sleep, and it can be helpful to ask how much sleep the patient obtains on a quiet vacation when he or she can sleep without restrictions. Some patients may think that a short amount of sleep is normal or advantageous, and they may not appreciate their biological need for more sleep, especially if coffee and other stimulants mask the sleepiness. A 2-week sleep log documenting the timing of sleep and daily level of alertness is diagnos tically useful and provides helpful feedback for the patient. Extending sleep to the optimal amount on a regular basis can resolve the sleepi ness and other symptoms. As with any lifestyle change, extending sleep requires commitment and adjustments, but the improvements in day time alertness make this change worthwhile. ■ ■SLEEP APNEA SYNDROMES Respiratory dysfunction during sleep is a common, serious cause of excessive daytime sleepiness as well as of disturbed nocturnal sleep. At least 24%

of middle-aged men and 9% of middle-aged women in the United States have a reduction or cessation of breathing dozens or more times each night during sleep, with 9% of men and 4% of women doing so more than a hundred times per night. These episodes may be due to an occlusion of the airway (obstructive sleep apnea), absence of respiratory effort (central sleep apnea), or a combination Obstructive sleep apnea (Chap. 308) Continuous positive airway pressure; upper airway surgery (e.g., uvulopalatopharyngoplasty); dental appliance; weight loss Narcolepsy Stimulants (e.g., modafinil, methylphenidate); rapid eye movement (REM) sleep-suppressing antidepressants (e.g., venlafaxine); pitolisant; solriamfetol; sodium oxybate Restless legs syndrome with or without periodic limb movements Treatment of predisposing condition; dopamine agonists (e.g., pramipexole, ropinirole); gabapentin; pregabalin; opiates Sleepiness due to a drug or medical condition Change medications, treat underlying condition, consider stimulants

of these factors. Failure to recognize and treat these conditions appro priately may reduce daytime alertness and increase the risk of sleeprelated motor vehicle crashes, depression, hypertension, myocardial infarction, diabetes, stroke, and mortality. Sleep apnea is particularly prevalent in overweight men and in the elderly, yet it is estimated to go undiagnosed in most affected individuals. This is unfortunate because several effective treatments are available. Readers are referred to Chap. 308 for a comprehensive review of the diagnosis and treat ment of sleep apnea.

■ ■NARCOLEPSY Narcolepsy is characterized by difficulty sustaining wakefulness, poor regulation of REM sleep, and disturbed nocturnal sleep. All patients with narcolepsy have excessive daytime sleepiness. This sleepiness is usually moderate to severe, and in contrast to patients with disrupted sleep (e.g., sleep apnea), people with narcolepsy usually feel well rested upon awakening and then feel tired throughout much of the day. They may fall asleep at inappropriate times, but then feel refreshed again after a nap. In addition, they often experience symptoms related to an intrusion of REM sleep characteristics into wakefulness. REM sleep is characterized by dreaming and muscle paralysis, and people with narcolepsy can have: (1) sudden muscle weakness without a loss of consciousness, which is usually triggered by strong emotions (cataplexy; Video 33-1); (2) dreamlike hallucinations at sleep onset (hypnagogic hallucinations) or upon awakening (hypnopompic hallucinations); and (3) muscle paralysis upon awakening (sleep paralysis). With severe cataplexy, an individual may be laughing at a joke and then suddenly collapse to the ground, immobile but awake for 1–2 min. With milder episodes, patients may have partial weakness of the face or neck. Narcolepsy is one of the more common causes of chronic sleepiness and affects about 1 in 2000 people in the United States. Narcolepsy typically begins between age 10 and 20; once established, the disease persists for life. PART 2 Cardinal Manifestations and Presentation of Diseases Narcolepsy is caused by loss of the hypothalamic neurons that pro duce the orexin neuropeptides (also known as hypocretins). Research in mice and dogs first demonstrated that a loss of orexin signaling due to null mutations of either the orexin neuropeptides or one of the orexin receptors causes sleepiness and cataplexy nearly identical to that seen in people with narcolepsy. Although genetic mutations rarely cause human narcolepsy, researchers soon discovered that patients with narcolepsy with cataplexy (now called type 1 narcolepsy) have very low or undetectable levels of orexins in their CSF, and autopsy studies showed a nearly complete loss of the orexin-producing neurons in the hypothalamus. The orexins normally promote long episodes of wakefulness and suppress REM sleep, and thus loss of orexin signal ing results in frequent intrusions of sleep during the usual waking episode, with REM sleep and elements of REM sleep at any time of day (Fig. 33-3). Patients with narcolepsy but no cataplexy (type 2 nar colepsy) usually have normal orexin levels

and may have partial loss of the orexin neurons or other yet uncharacterized causes of their exces sive daytime sleepiness. Healthy N3 N2 N1 REM Awake Narcolepsy N3 N2 N1 REM Awake 20:00 00:00 04:00 08:00 12:00 16:00 FIGURE 33-3 Polysomnographic recordings of a healthy individual and a patient with narcolepsy. The healthy individual has a long period or NREM sleep before entering REM sleep, but the individual with narcolepsy enters rapid eye movement (REM) sleep quickly at night and has moderately fragmented sleep. During the day, the healthy participant stays awake from 8:00 A.M. until midnight, but the patient with narcolepsy dozes off frequently, with many daytime naps that include REM sleep.

Extensive evidence suggests that an autoimmune process likely causes this selective loss of the orexin-producing neurons. Certain human leukocyte antigens (HLAs) can increase the risk of autoimmune disorders (Chap. 361), and narcolepsy has the strongest known HLA association. HLA DQB1*06:02 is found in >90% of people with type 1 narcolepsy, whereas it occurs in only 12–25% of the general popula tion. Researchers now hypothesize that in people with DQB1*06:02, an immune response against influenza, Streptococcus, or other infections may also damage the orexin-producing neurons through a process of molecular mimicry. This mechanism may account for the eight- to twelvefold increase in new cases of narcolepsy among children in Europe who received a particular brand of H1N1 influenza A vaccine (Pandemrix). In support of this hypothesis, people with type 1 narco lepsy have heightened T-cell responses against orexin peptides. On rare occasions, narcolepsy can occur with other neurologic dis orders such as anti-Ma2 paraneoplastic antibodies (Chap. 99), severe traumatic brain injury, tumors, or strokes that directly damage the orexin-producing neurons in the hypothalamus or their projections. Diagnosis Narcolepsy is most commonly diagnosed by relatively abrupt onset in a previously healthy individual of chronic sleepiness plus cataplexy or other symptoms. Narcoleptic patients report an over whelming desire to sleep, and often awake refreshed after a brief nap. Cataplexy is distinguished from many disorders that can cause feelings of weakness by sudden onset of postural weakness (e.g., slurred speech, dropping a cup, slumping into a chair) that is often triggered by strong emotions such as laughing at a joke, happy surprise at unexpectedly seeing a friend, or intense anger. Cataplexy occurs in about half of all narcolepsy patients, who are distinguished as narcolepsy type 1; when it occurs, cataplexy is diagnostically very helpful because it occurs in almost no other disorder. In contrast, hypnagogic hallucinations and sleep paralysis occur in both type 1 and type 2 narcolepsy patients, and occasionally in about 20% of the general population, and so are not as diagnostically specific. When narcolepsy is suspected, the diagnosis should be firmly established with a polysomnogram followed the next day by an MSLT. The polysomnogram helps rule out other causes of daytime sleepiness such as sleep apnea and establishes that the patient had adequate sleep the night before, and the MSLT provides essential, objective evidence of sleepiness plus REM sleep dysregulation. Across the five naps of the MSLT, most patients with narcolepsy will fall asleep in <8 min on average, and they will have episodes of REM sleep in at least two of the naps. Abnormal regulation of REM sleep is also manifested by the appearance of REM sleep within 15 min of sleep onset at night, which is rare in healthy individuals sleeping at their habitual bedtime. Stimu lants should be stopped 1 week before the MSLT, and antidepressants should be stopped 3 weeks prior, because these medications can sup press REM sleep. In addition, patients should be encouraged to obtain a fully adequate amount of sleep each night for the week prior to the test to eliminate any effects of insufficient sleep. Clock time

TREATMENT Narcolepsy The treatment of narcolepsy is symptomatic. Most patients with narcolepsy feel more alert after sleep, and they should be encour aged to get adequate sleep each night and to take a 15- to 20-min nap in the afternoon. This nap may be sufficient for occasional patients with mild narcolepsy, but most also require treatment with wake-promoting medications. Modafinil is often used because it has fewer side effects than amphetamines and a relatively long halflife; for most patients, 200–400 mg each morning is very effective. Methylphenidate (10–20 mg bid) and dextroamphetamine (10 mg bid) are also effective, but sympathomimetic side effects, anxiety, and the potential for abuse can be concerns. These medications are available in slow-release formulations, extending their duration of action and allowing easier dosing. Solriamfetol, a norepinephrine– dopamine reuptake inhibitor (75–150 mg daily), and pitolisant, a selective histamine 3 (H3) receptor antagonist (8.9–35.6 mg daily), also improve sleepiness and have relatively few side effects. Cataplexy is usually much improved with antidepressants that increase noradrenergic or serotonergic tone because these neu rotransmitters strongly suppress REM sleep and cataplexy. Venla faxine (37.5–150 mg each morning) and fluoxetine (10–40 mg each morning) are often quite effective. The tricyclic antidepressants, such as protriptyline (10–40 mg/d) or clomipramine (25–50 mg/d), are potent suppressors of cataplexy, but their anticholinergic effects, including sedation and dry mouth, make them less attractive.1 People with narcolepsy often have fragmented sleep at night, and sodium oxybate (gamma hydroxybutyrate), typically given at bed time and 3–4 h later, promotes more continuous slow wave sleep. Oxybates are also available in low-sodium and once-nightly ver sions. Oxybates are often very valuable in improving alertness and reducing cataplexy during the day, but at too high a dosage, they can produce excessive sedation, nausea, and confusion. 1No antidepressant has been approved by the U.S. Food and Drug Administration (FDA) for treating narcolepsy. ■ ■EVALUATION OF INSOMNIA Insomnia is the complaint of poor sleep and usually presents as dif ficulty initiating and/or maintaining sleep. People with insomnia are dissatisfied with their sleep and feel that it impairs their ability to function well in work, school, and social situations. Affected individu als often experience fatigue, decreased mood, irritability, malaise, and cognitive impairment. Chronic insomnia, lasting >3 months, occurs in about 10% of adults and is more common in women, older adults, people of lower socioeco nomic status, and individuals with medical, psychiatric, and substance abuse disorders. Acute or short-term insomnia affects >30% of adults and is often precipitated by stressful life events such as a major illness or loss, change of occupation, medications, and substance abuse. If the acute insomnia triggers maladaptive behaviors such as increased noc turnal light exposure, frequently checking the clock, or attempting to sleep more by napping, it can lead to chronic insomnia. Insomnia typically begins in adulthood, but many patients may be predisposed and report easily disturbed sleep predating the insomnia, suggesting that their sleep is lighter than usual. Clinical studies and animal models indicate that insomnia is associated with activation during sleep of brain areas normally active only during wakefulness. The polysomnogram is rarely used in the evaluation of insomnia, as it typically confirms the patient’s subjective report of long latency to sleep and numerous awakenings but usually adds little new informa tion. Many patients with insomnia have more fast (beta) activity in the EEG during sleep; this fast activity is normally present only dur ing wakefulness, which may explain why some patients report feeling awake for much of the night. The MSLT is rarely used in the evalu ation of insomnia because, despite their feelings of low energy, most

people with insomnia do not easily fall asleep during the day, and on the MSLT, their average sleep latencies are usually longer than normal.

Many factors can contribute to insomnia, and obtaining a careful history is essential so one can select therapies targeting the underly ing factors. The assessment should focus on identifying predisposing, precipitating, and perpetuating factors. Psychophysiological Factors Many patients with insomnia have negative expectations and conditioned arousal that interfere with sleep. These individuals may worry about their insomnia during the day and have increasing anxiety as bedtime approaches if they anticipate a poor night of sleep. While attempting to sleep, they may frequently check the clock, which only heightens anxiety and frustration. They may find it easier to sleep in a new environment rather than their bedroom, as it lacks the negative associations. Sleep Disorders CHAPTER 33 Inadequate Sleep Hygiene Patients with insomnia sometimes develop counterproductive behaviors that contribute to their insomnia. These can include daytime napping that reduces sleep drive at night; an irregular sleep-wake schedule that disrupts their circadian rhythms; use of wake-promoting substances (e.g., caffeine, tobacco) too close to bedtime; engaging in alerting or stressful activities close to bedtime (e.g., arguing with a partner, work-related emailing and texting while in bed, sleeping with a smartphone or tablet at the bedside); and routinely using the bedroom for activities other than sleep or sex (e.g., email, television, work), so the bedroom becomes associated with arousing or stressful feelings. Psychiatric Conditions About 80% of patients with psychiatric disorders have sleep complaints, and about half of all chronic insomnia occurs in association with a psychiatric disorder (Chap. 463). Depres sion is classically associated with early morning awakening, but it can also interfere with the onset and maintenance of sleep. Mania and hypomania can disrupt sleep and often are associated with substantial reductions in the total amount of sleep. Anxiety disorders can lead to racing thoughts and rumination that interfere with sleep and can be very problematic if the patient’s mind becomes active midway through the night. Panic attacks can arise from sleep and need to be distin guished from other parasomnias. Insomnia is common in schizophre nia and other psychoses, often resulting in fragmented sleep, less deep NREM sleep, and sometimes reversal of the day-night sleep pattern. Medications and Drugs of Abuse A wide variety of psychoactive drugs can interfere with sleep. Caffeine, which has a half-life of 6–9 h, can disrupt sleep for up to 8–14 h, depending on the dose, variations in metabolism, and an individual’s caffeine sensitivity. Insomnia can also result from use of prescription medications too close to bedtime (e.g., antidepressants, stimulants, glucocorticoids, theophylline). Conversely, withdrawal of sedating medications such as alcohol, narcotics, or ben zodiazepines can cause insomnia. Alcohol consumed just before bed can shorten sleep latency, but it often produces rebound insomnia 2–3 h later as it wears off. This same problem with sleep maintenance can occur with short-acting medications such as alprazolam or zolpidem. Medical Conditions A large number of medical conditions dis rupt sleep. Pain from rheumatologic disorders or a painful neuropathy commonly disrupts sleep. Some patients may sleep poorly because of respiratory conditions such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, congestive heart failure, or restrictive lung dis ease, and some of these disorders are worse at night due to circadian variations in airway resistance and postural changes in bed that can result in nocturnal dyspnea. Obstructive sleep apnea is an example of a respiratory disorder that only becomes a problem with loss of airway muscle tone during sleep. Many women experience poor sleep with the hormonal changes of menopause. Gastroesophageal reflux is also a common cause of difficulty sleeping. Approximately 60% of patients with long COVID report symptoms of insomnia. Neurologic Disorders Dementia (Chap. 31) is often associated with poor sleep, probably due to a variety of factors, including napping during the day, altered circadian rhythms, and perhaps a weakened

output of the brain’s sleep-promoting mechanisms. In fact, insomnia and nighttime wandering are some of the most common causes for institutionalization of patients with dementia, because they place a large burden on caregivers. Conversely, in cognitively intact elderly men, fragmented sleep and poor sleep quality are associated with subsequent cognitive decline. Patients with Parkinson’s disease may sleep poorly due to rigidity, dementia, urinary frequency, REM sleep behavior disorder, restless legs syndrome, and other factors. Fatal familial insomnia is a very rare neurodegenerative condition caused by mutations in the prion protein gene (Chap. 449), and although insom nia is a common early symptom, most patients present with other obvious neurologic signs such as dementia, myoclonus, dysarthria, or autonomic dysfunction.

PART 2 Cardinal Manifestations and Presentation of Diseases TREATMENT Insomnia Treatment of insomnia improves quality of life and can promote long-term health. With improved sleep, patients often report less daytime fatigue, improved cognition, and more energy. Treating the insomnia can also improve comorbid disease. For example, man agement of insomnia at the time of diagnosis of major depression often improves the response to antidepressants and reduces the risk of relapse. Sleep loss can heighten the perception of pain, so a simi lar approach is warranted in acute and chronic pain management. Gabapentin (100–300 mg before bedtime) can often reduce the pain and improve sleep in patients with chronic pain. The treatment plan should target all putative contributing fac tors: establish good sleep hygiene, treat medical disorders, and use behavioral therapies for anxiety and negative conditioning and pharmacotherapy and/or psychotherapy for psychiatric disorders. Behavioral therapies should be the first-line treatment, followed by judicious use of sleep-promoting medications if needed. TREATMENT OF MEDICAL AND PSYCHIATRIC DISEASE If the history suggests that a medical or psychiatric disease contrib utes to the insomnia, then it should be addressed by, for example, treating the pain or depression, improving breathing, and switching or adjusting the timing of medications. IMPROVE SLEEP HYGIENE Attention should be paid to improving sleep hygiene and avoiding counterproductive, arousing behaviors before bedtime. Patients should establish a regular bedtime and wake time, even on weekends, to help synchronize their circadian rhythms and sleep patterns. The amount of time allocated for sleep should not be more than their actual total amount of sleep. In the 30 min before bedtime, patients should establish a relaxing “wind-down” routine that can include a warm bath, listening to music, meditation, or other relaxation techniques. The bedroom should be off-limits to computers, televisions, radios, smartphones, videogames, and tablets. If an e-reader is used, the light should be adjusted for evening use (dimmer and reduced blue light) if possible, because light itself, especially in the blue spectrum, suppresses melato nin secretion and is arousing. Once in bed, patients should try to avoid thinking about anything stressful or arousing such as problems with relationships or work. If they cannot fall asleep within 20 min, it often helps to get out of bed and read or listen to relaxing music in dim light as a form of distraction from any anxiety, but “blue light,” especially from a cell phone, computer, or television, should be avoided. Table 33-2 outlines some of the key aspects of good sleep hygiene to improve insomnia. COGNITIVE BEHAVIORAL THERAPY Cognitive behavioral therapy (CBT) uses a combination of the techniques above plus additional methods to improve insomnia. A trained therapist may use cognitive psychology techniques to reduce excessive worrying about sleep and to reframe faulty beliefs about

TABLE 33-2 Methods to Improve Sleep Hygiene in Insomnia Patients HELPFUL BEHAVIORS BEHAVIORS TO AVOID Use the bed only for sleep and sex • If you cannot sleep within 20 min, Avoid behaviors that interfere with sleep physiology, including: • Napping, especially after 3:00 PM •

Attempting to sleep too early • Caffeine after lunchtime get out of bed and read or do other relaxing activities in dim light before returning to bed Make quality sleep a priority • Go to bed and get up at the same In the 2–3 h before bedtime, avoid: • Heavy eating • Smoking or alcohol • Vigorous exercise time each day • Ensure a restful environment (comfortable bed, bedroom quiet and dark) Develop a consistent bedtime routine. For example: • Prepare for sleep with 20–30 min When trying to fall asleep, avoid: • Solving problems • Thinking about life issues • Reviewing events of the day of relaxation (e.g., soft music, meditation, yoga, pleasant reading) • Take a warm bath the insomnia and its daytime consequences. The therapist may also teach the patient relaxation techniques, such as progressive muscle relaxation or meditation, to reduce autonomic arousal, intrusive thoughts, and anxiety. While sleep restriction may improve sleep continuity, chronic exposure to sleep restriction may have adverse effects on daytime performance. MEDICATIONS FOR INSOMNIA If insomnia persists after treatment of these contributing factors, pharmacotherapy is often used on a nightly or intermittent basis. A variety of sedatives can improve sleep. Antihistamines, such as diphenhydramine, are the primary active ingredient in most over-the-counter sleep aids. These may be of benefit when used intermittently but can produce tolerance and anticholinergic side effects such as dry mouth and constipation, which limit their use, particularly in the elderly. Benzodiazepine receptor agonists (BzRAs) are an effective and well-tolerated class of medications for insomnia (Chap. 463). BzRAs bind to the GABAA receptor and potentiate the postsynaptic response to GABA. GABAA receptors are found throughout the brain, and BzRAs may globally reduce neural activity and enhance the activity of specific sleep-promoting GABAergic pathways. Clas sic BzRAs include lorazepam, triazolam, and clonazepam, whereas newer agents such as zolpidem and zaleplon have more selective affinity for the α1 subunit of the GABAA receptor. Specific BzRAs are often chosen based on the desired duration of action. The most commonly prescribed agents in this family are zaleplon (5–20 mg), with a half-life of 1–2 h; zolpidem (5–10 mg) and triazolam (0.125–0.25 mg), with half-lives of 2–4 h; eszopiclone (1–3 mg), with a half-life of 5–8 h; and temazepam (15–30 mg), with a half-life of 8–20 h. Generally, side effects are uncommon when the dose is kept low and the serum concentration is minimized during the waking hours (by using the shortest-acting effective agent). For chronic insomnia, intermittent use is recommended, unless the consequences of untreated insomnia outweigh concerns regarding chronic use. The heterocyclic antidepressants (trazodone, amitriptyline,2 and doxepin) are the most commonly prescribed alternatives to BzRAs due to their lack of abuse potential and low cost (Chap. 463). Trazodone (25–100 mg) is used more commonly than the tricyclic antidepressants, because it has a much shorter half-life (5–9 h) and less anticholinergic activity. The orexin receptor antagonists suvorexant (10–20 mg), lembo rexant (5–10 mg), and daridorexant (25–50 mg) can also improve insomnia by blocking the wake-promoting effects of the orexin neuropeptides. These have medium to long half-lives and can pro duce morning sedation, and as they reduce orexin signaling, they

can rarely produce hypnagogic hallucinations and sleep paralysis (see narcolepsy section above). Medications for insomnia are now among the most commonly prescribed medications, but they should be used cautiously. All sed atives increase the risk of injurious falls and confusion in the elderly, and therefore, if needed, these medications should be used at the lowest effective dose. Morning sedation can interfere with driving and judgment, so when selecting a medication, one should consider the duration of action. Benzodiazepines carry a risk of addiction and abuse, especially in patients with a history of alcohol or seda tive abuse. In patients with depression, all sedatives can worsen the depression. Like alcohol, some sleep-promoting medications can worsen

sleep apnea. Sedatives can also produce complex behaviors during sleep, such as sleepwalking and sleep eating, especially at higher doses. 2Trazodone and amitriptyline have not been approved by the FDA for treating insomnia. ■ ■RESTLESS LEGS SYNDROME Patients with restless legs syndrome (RLS) report an irresistible urge to move the legs. Many patients report a creepy-crawly, tingly, or unpleas ant deep ache within the thighs or calves, and those with more severe RLS may have discomfort in the arms as well. For most patients with RLS, these dysesthesias and restlessness are much worse in the evening and first half of the night. The symptoms appear with inactivity and can make sitting still when traveling or watching a movie a miserable expe rience. The sensations are temporarily relieved by movement, stretch ing, or massage. This nocturnal discomfort usually interferes with sleep, and patients may report daytime sleepiness as a consequence. RLS is very common, affecting 5–10% of adults, and is more common in women and older adults. A variety of factors can cause RLS. Iron deficiency is the most com mon treatable cause, and iron replacement should be considered if the ferritin level is <75 ng/mL. RLS can also occur with peripheral neurop athies and uremia and can be worsened by pregnancy, caffeine, alcohol, antidepressants, lithium, neuroleptics, and antihistamines. Genetic factors contribute to RLS, and polymorphisms in a variety of genes (BTBD9, MEIS1, MAP2K5/LBXCOR, and PTPRD) have been linked to RLS, although as yet, the mechanism through which they cause RLS remains unknown. Roughly one-third of patients (particularly those with an early age of onset) have multiple affected family members. RLS is treated by addressing the underlying cause such as iron deficiency if present. Otherwise, treatment is symptomatic, and alpha-2-delta calcium channel ligands or dopamine agonists are used most frequently. Alpha-2-delta calcium channel ligands such as gabapentin (300–900 mg q7PM), gabapentin enacarbil (300–600 mg q5PM), and pregabalin (150–450 mg q7PM) are quite effective, and because they are also sedating and analgesic, they can be especially helpful in patients with concomitant pain, neuropathy, or anxiety. Agonists of dopamine D2/3 receptors such as pramipexole (0.25–0.5 mg q7PM) or ropinirole (0.5–4 mg q7PM) are usually quite effective, but about 25% of patients taking dopamine agonists develop augmenta tion, a worsening of RLS such that symptoms begin earlier in the day and can spread to other body regions. Other possible side effects of dopamine agonists include nausea, morning sedation, and increases in rewarding behaviors such as sex and gambling. Opioids and ben zodiazepines may also be of therapeutic value in refractory patients. Most patients with restless legs also experience PLMD, although the reverse is not the case. ■ ■PERIODIC LIMB MOVEMENT DISORDER PLMD involves rhythmic twitches of the legs that disrupt sleep. The movements resemble a triple flexion reflex with extensions of the great toe and dorsiflexion of the foot for 0.5–5.0 s, which recur every 20–40 s during NREM sleep, in episodes lasting from minutes to hours. PLMD is diagnosed by a polysomnogram that includes recordings of the ante rior tibialis and sometimes additional muscles. The EEG shows that

the movements of PLMD frequently cause brief arousals that disrupt sleep, sometimes resulting in insomnia and daytime sleepiness. PLMD can be caused by the same factors that cause RLS (see above), and the frequency of leg movements improves with the same medications used for RLS, including dopamine agonists. Genetic studies identified poly morphisms associated with both RLS and PLMD, suggesting that they may have a common pathophysiology.

■ ■PARASOMNIAS Parasomnias are abnormal behaviors or experiences that arise from or occur during sleep. A variety of parasomnias can occur during NREM sleep, from brief confusional arousals to sleepwalking and night terrors. The presenting complaint is usually related to the

behavior itself, but the parasomnias can disturb sleep continuity or lead to mild impairments in daytime alertness. Two main parasomnias occur in REM sleep: REM sleep behavior disorder (RBD) and nightmares. Sleep Disorders CHAPTER 33 Sleepwalking (Somnambulism) Patients affected by this dis order carry out automatic motor activities that range from simple to complex. Individuals may walk, urinate inappropriately, eat, exit the house, or drive a car with minimal awareness. It may be difficult to arouse the patient to wakefulness, and some individuals may respond to attempted awakening with agitation or violence. In general, it is saf est to lead the patient back to bed, at which point they will often fall back asleep. Sleepwalking arises from NREM stage N3 sleep, usually in the first few hours of the night, and the EEG initially shows the slow cortical activity of deep NREM sleep even when the patient is mov ing about. Sleepwalking is most common in children and adolescents, when deep NREM sleep is most abundant. About 15% of children have occasional sleepwalking, and it persists in about 1% of adults. Episodes are usually isolated but may be recurrent in 1–6% of patients. The cause is unknown, although it has a familial basis in roughly one-third of cases. Sleepwalking can be worsened by stress, alcohol, and insufficient sleep, which subsequently causes an increase in deep NREM sleep. These should be addressed if present. Small studies have shown some efficacy of antidepressants and benzodiazepines; relaxation techniques and hypnosis can also be helpful. Patients and their families should improve home safety (e.g., replace glass doors, remove low tables to avoid tripping) to minimize the chance of injury if sleepwalking occurs. Sleep Terrors This disorder occurs primarily in young children during the first few hours of sleep during NREM stage N3 sleep. The child often sits up during sleep and screams, exhibiting autonomic arousal with sweating, tachycardia, large pupils, and hyperventilation. The individual may be difficult to arouse and rarely recalls the episode on awakening in the morning. Treatment usually consists of reassuring parents that the condition is self-limited and benign, and like sleep walking, it may improve by avoiding insufficient sleep. Sleep Enuresis Bedwetting, like sleepwalking and night terrors, is another parasomnia that occurs during sleep in the young. Before age 5 or 6 years, nocturnal enuresis should be considered a normal feature of development. The condition usually improves spontane ously by puberty, persists in 1–3% of adolescents, and is rare in adult hood. Treatment consists of bladder training exercises and behavioral therapy. Symptomatic pharmacotherapy is usually accomplished in adults with desmopressin (0.2 mg qhs), oxybutynin chloride (5 mg qhs), or imipramine (10–25 mg qhs). Important causes of nocturnal enuresis in patients who were previously continent for 6–12 months include urinary tract infections or malformations, cauda equina lesions, emotional disturbances, epilepsy, sleep apnea, and certain medications. Sleep Bruxism Bruxism is an involuntary, forceful grinding of teeth during sleep that affects 10–20% of the population. The patient is usually unaware of the problem. The typical age of onset is 17–20 years, and spontaneous remission usually occurs by age 40. In many cases, the diagnosis is made during dental examination, damage is minor, and no treatment is indicated. In more severe cases, treatment with a mouth guard is necessary to prevent tooth injury. Stress management,

benzodiazepines, and biofeedback can be useful when bruxism is a manifestation of psychological stress.

REM Sleep Behavior Disorder (RBD) RBD (Video 33-2) is distinct from other parasomnias in that it occurs during REM sleep. The patient or the bed partner usually reports that the patient calls out and has agitated or violent behavior during sleep. If awakened during or by the event, the patient can often report a dream that matches the accompanying movements. During normal REM sleep,

nearly all nonrespiratory skeletal muscles are paralyzed, but in patients with RBD, dramatic limb movements such as punching or kicking lasting seconds to minutes occur during REM sleep, and it is not uncommon for the patient or the bed partner to be injured while enacting dream behaviors. PART 2 Cardinal Manifestations and Presentation of Diseases The prevalence of RBD increases with age, afflicting about 2% of adults aged >70, and is reported more often in men. Within 12 years of disease onset, half of RBD patients develop a synucleinopathy such as Parkinson's disease (Chap. 446), dementia with Lewy bodies (Chap. 445), or occasionally multiple system atrophy (Chap. 451), and >90% develop a synucleinopathy by 25 years. Patients with a latent synucleinopathy can be distinguished from those with other causes of symptomatic RBD by detection of alpha-synuclein aggre gates in spinal fluid or in peripheral nerves in skin biopsy. RBD can occur in patients taking antidepressants, and in some, these medica tions may unmask this early indicator of neurodegeneration. Synucle inopathies probably cause neuronal loss in brainstem regions that regulate muscle paralysis during REM sleep, and loss of these neurons permits movements to break through during REM sleep. RBD also occurs in about 30% of people with narcolepsy, but the underlying cause is probably different, as they seem to be at no increased risk of a neurodegenerative disorder. Many patients with RBD have sustained improvement with melato nin at doses up to 10 mg nightly. Clonazepam (0.5–2.0 mg qhs)3 also prevents attacks, but as with all benzodiazepines, it can increase the risk of falls and confusion at night. ■ ■CIRCADIAN RHYTHM SLEEP DISORDERS A subset of patients presenting with either insomnia or hypersomnia may have a disorder of sleep timing rather than sleep generation. Disor ders of sleep timing can be either inherent (i.e., due to an abnormality of circadian pacemaker[s]) or environmental/behavioral (i.e., due to a disruption of environmental synchronizers). The therapeutic goal is to entrain the circadian rhythm of sleep propensity to the appropriate behavioral phase. Delayed Sleep-Wake Phase Disorder DSWPD is character ized by: (1) sleep onset and wake times persistently later than desired; (2) actual sleep times at nearly the same clock hours daily; and (3) if conducted at the habitual delayed sleep time, essentially normal sleep on polysomnography (except for delayed sleep onset). About half of patients with DSWPD exhibit an abnormally delayed endogenous circadian phase, which can be assessed by measuring the onset of secretion of melatonin in either the blood or saliva; this is best done in a dimly lit environment as light suppresses melatonin secretion. In healthy people, dim-light melatonin onset (DLMO) typically occurs about 8:00–9:00 P.M. (i.e., about 1–2 h before habitual bedtime), but in DSWPD patients, DLMO occurs later in the evening than normal, which helps distinguish DSWPD from other forms of sleep-onset insomnia. Patients tend to be young adults. The delayed circadian phase could be due to: (1) an abnormally long, genetically determined intrinsic period of the endogenous circadian pacemaker; (2) reduced phase-advancing capacity of the pacemaker; (3) slower buildup of homeostatic sleep drive during wakefulness; or (4) an irregular prior sleep-wake schedule, characterized by frequent nights when the patient chooses to remain awake while exposed to artificial light well past mid night (for personal, social, school, or work reasons). In most cases, it is difficult to distinguish among these factors, as both patients with either 3No medications have been approved by the FDA for the treatment of RBD.

a behaviorally induced or biologically driven circadian phase delay may exhibit a similar circadian phase delay in DLMO, and both factors make it difficult to fall asleep at the desired hour. DSWPD is a chronic condition that can persist for years and may not respond to attempts to reestablish normal bedtime hours. Typical treatment is phototherapy with blue-enriched light during the morning hours and/or melatonin administration in the evening hours, although the relapse rate is

high. Advanced Sleep-Wake Phase Disorder Advanced sleep-wake phase disorder (ASWPD) is the converse of DSWPD. Most commonly, this syndrome occurs in older people, 15% of whom report that they cannot sleep past 5:00 A.M., with twice that number complaining that they wake up too early at least several times per week. Patients with ASWPD are sleepy during the evening hours, even in social settings. Sleep-wake timing in ASWPD patients can interfere with a normal social life. Patients with this circadian rhythm sleep disorder can be distinguished from those who have early wakening due to insomnia because ASWPD patients show early onset of dim-light melatonin secretion. In addition to age-related ASWPD, an early-onset familial variant of this condition has also been reported. In two families in which ASWPD was inherited in an autosomal dominant pattern, the syndrome was due to missense mutations in a circadian clock component (in the casein kinase binding domain of PER2 in one family, and in casein kinase I delta in the other) that shortens the circadian period. Patients with ASWPD may benefit from bright light and/or blue-enriched pho totherapy during the evening hours to reset the circadian pacemaker to a later hour. Non-24-h Sleep-Wake Rhythm Disorder Non-24-h sleepwake rhythm disorder (N24SWD) most commonly occurs when the primary synchronizing input (i.e., the light-dark cycle) from the envi ronment to the circadian pacemaker is lost (as occurs in many blind people with no light perception), and the maximal phase-advancing capacity of the circadian pacemaker in response to nonphotic cues cannot accommodate the difference between the 24-h geophysical day and the intrinsic period of the patient’s circadian pacemaker, resulting in loss of entrainment to the 24-h day. The sleep of most blind patients with N24SWD is restricted to the nighttime hours due to social or occupational demands. Despite this regular sleep-wake schedule, affected patients with N24SWD are nonetheless unable to maintain a stable phase relationship between the output of the nonentrained circa dian pacemaker and the 24-h day. Therefore, most blind patients with no light perception present with intermittent bouts of insomnia. When the blind patient’s endogenous circadian rhythms are out of phase with the local environment, nighttime insomnia coexists with excessive day time sleepiness. Conversely, when the endogenous circadian rhythms of those same patients are in phase with the local environment, symp toms remit. The interval between symptomatic phases may last several weeks to several months in blind patients with N24SWD, depending on the difference between the period of the underlying nonentrained rhythm and the 24-h day. Nightly administration of low-dose (0.5 mg) melatonin or a melatonin receptor agonist may improve sleep and, in some cases, induce synchronization of the circadian pacemaker. In sighted patients, N24SWD can be caused by self-selected exposure to artificial light that inadvertently entrains the circadian pacemaker to a >24-h schedule, and these individuals present with an incremental pattern of successive delays in sleep timing, progressing in and out of phase with local time—a clinical presentation that is seldom seen in blind patients with N24SWD. Shift-Work Disorder More than 7 million people in the United States regularly work at night, either on a permanent or rotating schedule. Many more begin the commute to work or school between 4:00 A.M. and 7:00 A.M., requiring them to commute and then work during a time of day that they would otherwise be asleep. In addition, each week, millions of “day” workers and students elect to remain awake at night or awaken very early in the morning to work or study to meet work or school deadlines, drive long distances, compete in sporting

events, or participate in recreational activities. Such schedules can result in both sleep loss and misalignment of circadian rhythms with respect to the sleep-wake cycle. The circadian timing system usually fails to adapt successfully to the inverted schedules required by overnight work or the phase advance required by early morning (4:00 A.M. to 7:00 A.M.) start times, par ticularly if

the shift worker reverts to a normal day-night schedule on days off. This leads to a misalignment between the desired work-rest schedule and the output of the pacemaker, resulting in disturbed day time sleep in most such individuals. Excessive work hours (per day or per week), insufficient time off between consecutive days of work or school, and frequent travel across time zones may be contribut ing factors. Sleep deficiency, increased length of time awake prior to work, and misalignment of circadian phase impair alertness and performance, increase reaction time, and increase risk of performance lapses, thereby resulting in greater safety hazards among night workers and other sleep-deprived individuals. Sleep disturbance nearly doubles the risk of a fatal work accident. Similarly, the risk of sleep-related, fatal-to-the-driver highway crashes is highest in the early morning and late afternoon hours, coincident with bimodal peaks in the daily rhythm of sleep tendency. An expert consensus panel has concluded that individuals who have slept <2 h in the prior 24 h are unfit to drive a motor vehicle. In addition, long-term night-shift workers may have higher rates of breast, colorectal, and prostate cancer and of cardiac, gastrointestinal, metabolic, and reproductive disorders. The World Health Organization has added night-shift work to its list of probable carcinogens. Both circadian rhythms and sleep deficiency contribute to this risk. Physicians who work prolonged shifts, especially intermittent overnight shifts, constitute another group of workers at greater risk for accidents and other adverse consequences of lack of sleep and mis alignment of the circadian rhythm. Recurrent scheduling of resident physicians to work shifts of ≥24 consecutive hours impairs psychomo tor performance to a degree that is comparable to alcohol intoxica tion, doubles the risk of attentional failures among intensive care unit resident physicians working at night, and increases the risk of serious medical errors in intensive care units, including a fivefold increase in the risk of serious diagnostic mistakes. Some 20% of hospital resident physicians report making a fatigue-related mistake that injured a patient, and 5% admit making a fatigue-related mistake that resulted in the death of a patient. Moreover, working for >24 consecutive hours increases the risk of percutaneous injuries and more than doubles the risk of motor vehicle crashes during the commute home. For these reasons, a National Academy of Medicine report concluded that the practice of scheduling resident physicians to work for >16 consecutive hours without sleep is hazardous for both resident physicians and their patients. Of individuals scheduled to work at night or in the early morning hours, 5–15% have much greater-than-average difficulties remaining awake during night work and sleeping during the day; these individu als are diagnosed with chronic and severe shift-work disorder (SWD). Patients with this disorder have a level of excessive sleepiness during work at night or in the early morning and insomnia during day sleep that the physician judges to be clinically significant; the condition is associated with an increased risk of sleep-related accidents and with some of the illnesses associated with night-shift work. Patients with chronic and severe SWD are profoundly sleepy at work. In fact, their sleep latencies during night work average just 2 min, comparable to mean daytime sleep latency durations of patients with narcolepsy or severe sleep apnea. TREATMENT Shift-Work Disorder Caffeine is frequently used by night workers to promote wakeful ness. However, it cannot forestall sleep indefinitely, and it does not shield users from sleep-related performance lapses. Postural changes, exercise, and strategic placement of nap opportunities can

sometimes temporarily reduce the risk of fatigue-related perfor mance lapses. Properly timed exposure to blue-enriched light or bright white light can directly enhance alertness and facilitate more rapid adaptation to night-shift work.

Modafinil (200 mg) or armodafinil (150 mg) 30–60 min before the start of an 8-h overnight shift is an effective treatment for the excessive sleepiness during night work in patients with SWD.

Although treatment with modafinil or armodafinil significantly improves performance and reduces sleep propensity and the risk of lapses of attention during night work, affected patients remain excessively sleepy. Sleep Disorders CHAPTER 33 Fatigue risk management programs for night-shift workers should promote education about sleep, increase awareness of the hazards associated with sleep deficiency and night work, and screen for common sleep disorders. Work schedules should be designed to minimize: (1) exposure to night work; (2) the frequency of shift rotations; (3) the number of consecutive night shifts; and (4) the duration of night shifts. Jet Lag Disorder Each year, >60 million people fly from one time zone to another, often resulting in excessive daytime sleepiness, sleeponset insomnia, or frequent arousals from sleep, particularly in the lat ter half of the night. The syndrome is transient, typically lasting 2–14 d depending on the number of time zones crossed, the direction of travel, and the traveler's age and phase-shifting capacity. Travelers who spend more time outdoors at their destination reportedly adapt more quickly than those who remain in hotel or seminar rooms, presumably due to brighter (outdoor) light exposure. Avoidance of antecedent sleep loss or napping in the afternoon prior to overnight travel can reduce the difficulties associated with extended wakefulness. Laboratory studies suggest that low doses of melatonin can enhance sleep efficiency, but only if taken when endogenous melatonin concentrations are low (i.e., during the biologic daytime). In addition to jet lag associated with travel across time zones, many patients report a behavioral pattern that has been termed social jet lag, in which bedtimes and wake times on weekends or days off occur 3–4 h or more later than during the week. Such recurrent displace ment of the timing of the sleep-wake cycle is common in adolescents and young adults and is associated with delayed circadian phase, sleep-onset insomnia, excessive daytime sleepiness, poorer academic performance, and increased risk of both obesity and depressive symptoms. ■ ■MEDICAL IMPLICATIONS OF CIRCADIAN RHYTHMICITY Prominent circadian variations have been reported in the incidence of acute myocardial infarction, sudden cardiac death, and stroke, the leading causes of death in the United States. Platelet aggregability is increased in the early morning hours, coincident with the peak inci dence of these cardiovascular events. Recurrent circadian disruption combined with chronic sleep deficiency, such as occurs during nightshift work, is associated with increased plasma glucose concentrations after a meal due to inadequate pancreatic insulin secretion. Nightshift workers with elevated fasting glucose have an increased risk of progressing to diabetes. Blood pressure of night workers with sleep apnea is higher than that of day workers. A better understanding of the possible role of circadian rhythmicity in the acute destabilization of a chronic condition such as atherosclerotic disease could improve the understanding of its pathophysiology. Diagnostic and therapeutic procedures may also be affected by the time of day at which data are collected. Examples include blood pressure, body temperature, the dexamethasone suppression test, and plasma cortisol levels. The timing of administration of drugs such as chemotherapy can affect both their toxicity and effectiveness. Anes thetic agents are particularly sensitive to time-of-day effects. Finally, the physician must be aware of the public health risks associated with the ever-increasing demands made by the 24/7 schedules in our roundthe-clock society.

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