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Sleep Neurology

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DENOTES *CONTINUUM* AUDIO INTERVIEW

DENOTES VIDEO CONTENT

SELECTED TOPICS IN NEUROLOGY PRACTICE

SELF-ASSESSMENT AND CME

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EDITOR'S PREFACE

A Brain Health Imperative

I apologize to my patients when I'm running behind in clinic. It's a sign of respect for their time and lets them know I'm aware of the delay (and trying my best). But if we're being honest, even when we're on time, neurologists are usually late. By the time we evaluate most patients with symptomatic presentations in the clinic or the hospital, we are seeing the neurologic manifestations of underlying disorders that have developed over months, years, or decades. We've all seen patients with acute stroke who have had years of latent hypertension, or a patient with new disabling neuropathy after decades of diabetes. The simple fact is that we don't conventionally have the opportunity for early intervention to maintain brain health rather than treat neurologic disease. This issue of *Continuum*, dedicated to sleep neurology, gives us exactly that opportunity.

Sleep neurology occupies a distinctive corner of our specialty. Sleep is not a disorder. It's a ubiquitous yet mysterious state in which we spend almost one-third of our lives. We now know that disorders of sleep provide a window into neurologic function and dysfunction. Close observation of sleep can serve as a crystal ball predicting future neurologic problems, illustrated by the connection between dream enactment and the development of synucleinopathies. The identification and treatment of sleep disorders can reduce the risk of future neurologic catastrophe, as in obstructive sleep apnea and stroke. A better understanding of sleep physiology can give us meaningful pathophysiologic insight into enigmatic neurodegenerative disorders like Alzheimer disease. An appreciation of sleep neurology yields an uncommon opportunity in our field: a means for prospective maintenance of brain health.

In this Sleep Neurology issue of *Continuum*, you will find a definitive overview of an evolving field. Serving as guest editor for this issue, Dr Anita Shelgikar has assembled an authoritative list of topics, authors, and articles, covering everything a neurologist needs to know about sleep physiology and pathophysiology. Dr Pablo R. Castillo introduces the issue with an article that will satisfy any reader looking to binge on the intricate neuroanatomy and neurophysiology of a complex state. Next, Dr Samuel A. Taylor Jr provides a thoughtful approach to sleep disorders in the clinical neurology setting. Drs Margaret Blattner and Kiran Maski thoroughly review central disorders of hypersomnolence including narcolepsy and idiopathic hypersomnia. In her article on obstructive sleep apnea, Dr Karin G. Johnson covers everything neurologists need to know about a major population health problem and source of neurologic morbidity. The enigmas of REM and non-REM parasomnias are wonderfully summarized by Drs Roneil Malkani and Andrew R. Spector in their respective articles on these essential topics. Dr Meena Khan delivers a complete discussion of nocturnal movement disorders, including the highly prevalent restless legs syndrome. Disruptive circadian rhythm disorders are carefully outlined in the article authored by Dr Flavia B. Consens. Drs Scott Kutscher and Christine Juang explain the latest developments in the treatment of insomnia.

Neurologists should be familiar with the sleep disturbances associated with neurologic disorders, and these are comprehensively reviewed by Dr Joyce K. Lee-Iannotti. The distinctive presentations and management of sleep disorders in childhood deserve their own review, and Dr Althea Robinson Shelton's article provides a superbly written discussion of pediatric sleep neurology. In the last of the clinical review articles, Dr Oleg Y. Chernyshev outlines the potentially disastrous consequences of chronic sleep deprivation.

As always, after reading or listening to the content in this issue, subscribers can obtain up to 20 AMA PRA Category 1 Credits™ toward self-assessment CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program [Section 3] of the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada with our posttest, written for the print issue by Drs D. Joanne Lynn and Allyson R. Zazulia.

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We are proud of *Continuum*'s longstanding commitment to delivering high-quality clinical education for neurologists and others who care for neurology patients. We are also aware that there are many nonclinical topics that are of central importance to clinicians and patients. For this reason, I am thrilled to announce a new *Continuum* article series called Selected Topics in Neurology Practice. These articles will have a consistent presence in *Continuum* issues and discuss a diverse range of topics, including health disparities and equity, systems of care, health policy, medical economics, quality improvement, medical ethics, advocacy, and likely others. Under the guidance of Dr Pearce Korb, our Associate Editor of Selected Topics in Neurology Practice, the articles in this series will complement the issues to which they are assigned.

Dr Anita Shelgikar has assembled an authoritative list of topics, authors, and articles, covering everything a neurologist needs to know about sleep physiology and pathophysiology.

The inaugural Selected Topics in Neurology Practice article is included with this issue, and I can't imagine a more fitting topic or authors to lead off the series. Health policy clearly has broad implications for medicine and neurology; given the pervasive role sleep plays in our lives, outwardly non-health-related policies have unintended effects on sleep and therefore population health. In their article, "Implications of Sleep Health Policy: Daylight Saving and School Start Times," Drs Karin G. Johnson (pulling double duty in this issue) and Beth A. Malow provide a wonderful summary of how time zone, Daylight Saving, and school start time policies lead to negative health consequences on a large scale. In addition, they review past and ongoing advocacy efforts to improve policies that relate to sleep health.

I can't overstate my gratitude to Dr Shelgikar for her leadership in creating and refining this issue, and to our authors for sharing their clinical expertise. This issue contains exciting new changes for *Continuum*, and thanks to our editorial staff and leadership team we have more changes coming soon. Foremost, I'm grateful to you, our readers and listeners, without whom we would not have this wonderful journal to share.

—LYELL K. JONES JR, MD, FAAN
EDITOR-IN-CHIEF

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Clinical Neurobiology of Sleep and Wakefulness

By Pablo R. Castillo, MD, FAAN

ABSTRACT

OBJECTIVE: **This article focuses on novel neuronal mechanisms of sleep and wakefulness and relates basic science developments with potential translational implications in circadian neurobiology, pharmacology, behavioral factors, and the recently integrated potential pathways of sleep-related motor inhibition.**

LATEST DEVELOPMENTS: **During the past decade, remarkable advances in the molecular biology of sleep and wakefulness have taken place, opening a promising path for the understanding of clinical sleep disorders. Newly gained insights include the role of astrocytes in sleep brain homeostasis through the glymphatic system, the promotion of memory consolidation during states of reduced cholinergic activity during slow wave sleep, and the differential functions of melatonin receptors involving regulation of both circadian rhythm and sleep initiation. Ongoing investigations exploring sleep and circadian rhythm disruptions are beginning to unlock pathophysiologic aspects of neurologic, psychiatric, and medical disorders.**

ESSENTIAL POINTS: **An understanding of sleep and circadian neurobiology provides coherent and biologically credible approaches to treatments, including the identification of potential targets for neuromodulation.**

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Castillo discusses the unlabeled/investigational use of trazodone for the treatment of insomnia.

INTRODUCTION

The discovery of localized sleep and wake centers in the brain will remain elusive. The complexity of sleep as a reversible use-dependent process involving the synchronization of multiple neuronal assemblies, along with the recognition that sleep can occur within localized cortical regions, suggest that the presence of a unique sleep-center generator may not be required for sleep to occur.[1] Ascribing any complex behavior as the result of single excitatory or inhibitory neurotransmitter activity has the potential to misguide progress toward understanding the neurobiology of clinical sleep disorders. Additionally, any assumptions from studies done in predominantly nocturnal animals must be considered with prudence when applied to human physiology.

FUNDAMENTALS OF SLEEP AND WAKEFULNESS

Sleep does not serve a single physiologic function; rather, many essential functions are supported by the physiologic state of sleep, including organism

development, metabolism, glymphatic system brain waste clearance, immune response, cognition, and the synaptic plasticity necessary for mechanisms of memory consolidation.

The sleep-wake cycle is under the influence of the two-process model, namely, the homeostatic drive or sleep propensity (Process S) and the circadian alerting signal (Process C) that originates from the suprachiasmatic nucleus circuitry. The main drivers of Process S are the accumulation of adenosine and the solar daytime activation of the melanopsin system (discussed in the section on circadian rhythms, sleep, and metabolism); both drivers appear necessary to facilitate the buildup of sleep propensity during prolonged wakefulness.

Adenosine acts through several G-protein coupled receptor subtypes: A1, A2a, A2b, and A3. The A1 receptors are expressed at high levels throughout the brain, particularly in the cortex, hippocampus, and thalamus. The A2a subtype is profusely expressed in the medium spiny γ-amino butyric acid–mediated (GABA-ergic) neurons projecting to the external segment of the globus pallidus. Genes expressed specifically in the medium spiny GABA-ergic neurons are associated with insomnia (FIGURE 1-1).[2]

The activation of A1 receptors promotes sleep by inhibiting wake-active cholinergic neurons of the basal forebrain and ascending arousal system (or ascending reticular activating system) components, including the pedunculopontine nucleus and laterodorsal tegmentum. A1 receptor activation can also have direct sleep-enhancing effects on the thalamocortical system and excitatory adenosine A2A receptors in the core region of the nucleus accumbens, which induces slow-wave sleep in mice.[3,4] Cholinergic neurons in the basal forebrain nucleus of Meynert are tonically inhibited by adenosine.

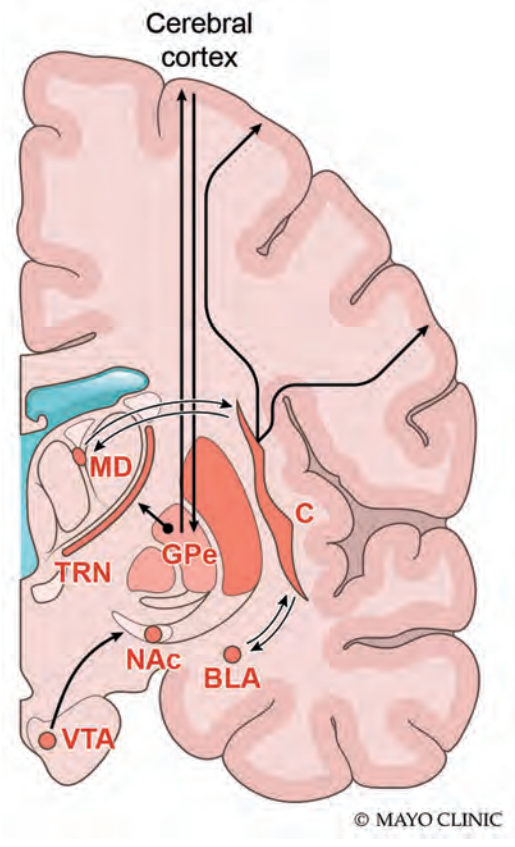

FIGURE 1-1
Basal ganglia networks showing prominent connectivity between the external segment of the globus pallidus (GPe) and other sleep-associated regions including the nucleus accumbens core (NAc), thalamic reticular nucleus (TRN), and prefrontal cortex. Additionally, the claustrum (C) displays reciprocal connections with thalamic medial dorsal nuclei (MD) and the basolateral amygdala (BLA), a region functionally related to the transition from slow-wave sleep to rapid eye movement (REM) sleep. Ventral tegmental area (VTA) dopaminergic projections to the NAc promote the transition from sleep to wakefulness.

Adenosine receptors are the main target of caffeine antagonism. At high concentrations, caffeine has other molecular targets including phosphodiesterase and causes GABA receptor inhibition.[5] Furthermore, antagonism of adenosine A1 receptors may lower seizure threshold by increasing the activity of excitatory neurotransmitters.[6-8]

Neuronal Assemblies and Circuit Interactions of Sleep and Wakefulness

The concept of a wake-sleep switch is based on reciprocal inhibition of the ascending arousal system and the sleep-promoting region of the hypothalamus named the ventrolateral preoptic (VLPO) nucleus. The flip-flop concept ascribes stability (mediated by the orexin [hypocretin] system) to the states of sleep and wakefulness, reducing the possibility of prolonged intermediate states. The wake-sleep flip-flop switch has been comprehensively described in the literature and has been the focus of extensive investigations.[9] However, questions remain about its anatomical presence and influence in the human brain.

The rodent preoptic area, which includes the median preoptic nucleus and the VLPO nucleus, is a sleep-active region that inhibits the ascending arousal system. The VLPO nucleus coexpresses GABA and the inhibitory neuropeptide galanin. The VLPO nucleus also contains glutamate-releasing neurons whose activation suppresses sleep. Unexpectedly, the integrity of the VLPO nucleus is not necessary for the loss of consciousness induced by some general anesthetics. Furthermore, high-frequency stimulation of the rodent preoptic area paradoxically causes wakefulness rather than sleep.[10]

Two galanin-expressing populations are present in the VLPO nucleus: the VLPO "core" or "cluster," thought to promote non–rapid eye movement (non-REM) sleep, and the "extended" VLPO nucleus linked to the regulation of REM sleep.[11] The precise location of a human homologue of the rodent VLPO nucleus remains uncertain. Neurons in the hypothalamic intermediate nucleus have similarities to the rodent VLPO nucleus, including their location in the chiasmatic region and the expression of galanin.[12]

Sleep Architecture: Non-REM and REM Sleep

The four stages of sleep identified in adults are non-REM stages 1, 2, and 3 and REM sleep. Each stage of sleep has characteristic electrophysiologic signatures. Non-REM stage 1 (N1) sleep is characterized by slow rolling eye movements, vertex sharp waves, and diffuse EEG slowing to 4 Hz to 7 Hz. Sleep spindles and K complexes are a hallmark of non-REM stage 2 (N2) sleep. The K complex is a type of slow wave, representing the largest physiologic event in human EEG recordings. K complexes may occur spontaneously or in response to a stimulus. The sharp onset of K complexes provides wide cortical synchronization, thus possibly coupling other slow-wave sleep–related oscillatory activities. K complexes show an EEG voltage decline with advancing age. Both K complexes and sleep spindles are lacking in the EEGs of patients with fatal familial insomnia. Slow-wave sleep, also known as deep sleep, delta sleep, or non-REM stage 3 (N3) sleep, is associated with the presence of silent states (down states) in cortical neurons. These silent states are periods that provide an opportunity for widespread synaptic preservation, whereas wakefulness is associated with increased synaptic strength and energy utilization. Slow-wave sleep may allow for the recalibration of neural circuits by favoring synaptic downscaling, ensuring sustainable synaptic homeostasis.[13] Moreover, during slow-wave sleep,

thalamocortical networks become relatively unresponsive, thus potentially preventing interference from external sensory inputs. Disorders of arousal such as sleepwalking and sleep terrors emerge from slow-wave sleep. It has been proposed that brain waste removal takes place during sleep via the glymphatic system, with aquaporin-4 channels facilitating astrocyte water transport. For information on the glymphatic system, refer to the article "Sleep Deprivation and Its Consequences," by Oleg Y. Chernyshev, MD, PhD,[14] in this issue of *Continuum*.

REM sleep is subdivided into microstates of phasic and tonic REM sleep. Phasic REM sleep is characterized by bursts of saccadic eye movements, myoclonic twitches of skeletal muscles, and a low-amplitude, high-frequency EEG pattern that often contains characteristic sawtooth waves. Tonic REM sleep is identified by longer, more quiescent periods interspersed between episodes of phasic REM sleep.[15] The glutamatergic REM-on neurons of the sublaterodorsal tegmental nucleus are key for REM sleep generation. The sublaterodorsal tegmental nucleus, located in the pons, is the brain region that triggers REM sleep atonia via stimulation of both the ventromedial medulla and the spinal interneurons that directly inhibit motor neurons via GABA and glycinergic projections.[16] Sublaterodorsal tegmental nucleus neurons become active when GABA-ergic input is reduced during wakefulness and slow-wave sleep. The sublaterodorsal tegmental nucleus and ventromedial medulla constitute the REM sleep atonia circuit; lesions in this area prevent physiologic REM sleep paralysis, which results in REM sleep without atonia. REM sleep without atonia can be triggered in various disease states (such as synucleinopathies) or exacerbated by different drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), mirtazapine, venlafaxine, and beta-blockers.[17]

Cholinergic neurons in the pedunculopontine tegmentum and laterodorsal tegmentum region are also REM-on cells, which project to the thalamus and basal forebrain regions and contribute to the generation of a low-amplitude, fast, desynchronized activity seen on scalp EEG during REM sleep that paradoxically resembles wakefulness.[18] Orexin (hypocretin) may have a role in REM sleep stabilization; a portion of orexin (hypocretin) neurons inhibit REM sleep by sending input to REM-off (REM-suppressing) neurons in the locus coeruleus, ventrolateral periaqueductal gray, and dorsal raphe nuclei, while other orexin (hypocretin) neurons exhibit REM sleep–related activation.[19] The activation of glutamatergic melanin-concentrating hormone from the lateral hypothalamus during REM sleep stabilizes and extends the duration of REM sleep episodes.[20] The basolateral amygdala contributes to the slow-wave sleep–to–REM sleep transition and also sends extensive GABA-ergic projections to brainstem regions that promote waking muscle tone and may trigger cataplexy in response to emotions in patients with narcolepsy.

The membrane potential of the thalamocortical neurons determines two patterns of discharge of the thalamocortical networks: (1) tonic firing of REM sleep and wakefulness and (2) an oscillatory burst-firing mode that occurs during slow-wave sleep. When the thalamocortical neurons are hyperpolarized, T-type calcium channels (blocked by the antiepileptic drug ethosuximide) are activated, with a promotion of burst firing and the generation of spindle oscillations at 7 Hz to 14 Hz that are transmitted to the cortex.[21] Spindles synchronize with hippocampal activity

KEY POINTS

- Caffeine promotes wakefulness primarily through antagonism of adenosine receptors.
- During slow-wave sleep, thalamocortical networks become relatively unresponsive, potentially preventing interference from external sensory inputs. Disorders of arousal such as sleepwalking and sleep terrors emerge from slow-wave sleep.
- The sublaterodorsal tegmental nucleus and ventromedial medulla constitute the rapid eye movement (REM) sleep atonia circuit; lesions in this area prevent physiologic REM sleep paralysis, which results in REM sleep without atonia.
- REM sleep without atonia can be triggered in various disease states (such as synucleinopathies) or exacerbated by different drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), mirtazapine, venlafaxine, and beta-blockers.
- A portion of orexin (hypocretin) neurons inhibit REM sleep by sending input to REM-off (REM-suppressing) neurons in the locus coeruleus, ventrolateral periaqueductal gray, and dorsal raphe nuclei, while other orexin (hypocretin) neurons exhibit REM sleep–related activation.

(FIGURE 1-2), pointing to a role for spindles in sleep-dependent memory consolidation.[22]

The ascending arousal system modifies the activity of thalamocortical neurons by sending modulatory cholinergic and monoaminergic inputs, which affect thalamocortical neuronal firing patterns. Acetylcholinergic input from the pedunculopontine nucleus depolarizes the thalamocortical neurons and promotes the transition from the burst-firing mode of slow-wave sleep to a faster tonic mode that is characteristic of wakefulness and REM sleep. Acetylcholine also elicits a muscarinic M2 receptor–mediated inhibition of thalamic reticular nucleus neurons. The combined effect results in the suppression of both spindle and slow-wave oscillations, while facilitating faster theta-band and gamma-band activity.

The thalamic medial dorsal nucleus has extensive projections with the prefrontal cortex. The thalamic medial dorsal nucleus participates in thalamic sleep-wake regulation, but its specific role in sleep promotion

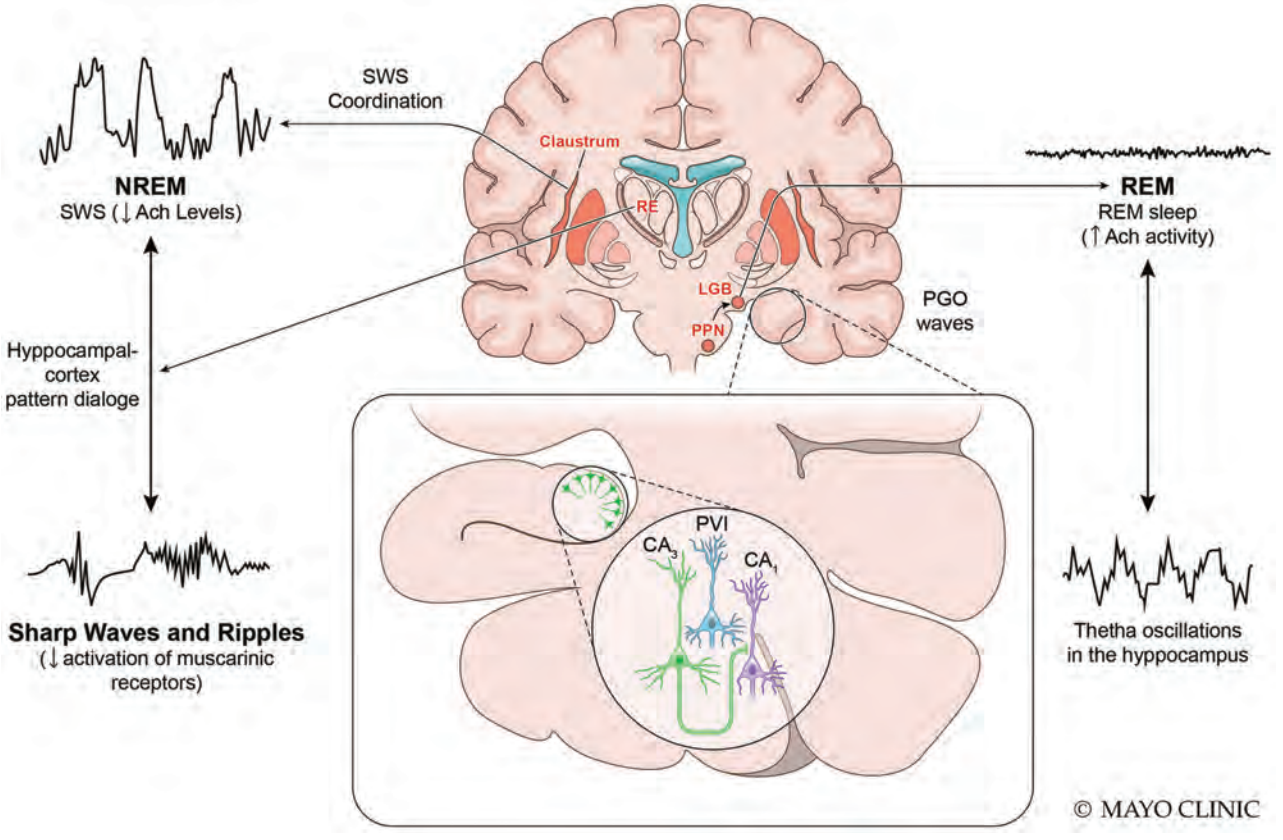

FIGURE 1-2

Memory circuits, including state-dependent connectivity and the neuroanatomical networks involved. Intertwined sharp-wave ripples and non–rapid eye movement (NREM) slow-wave sleep (SWS) dialogue likely participates in episodic memory consolidation. The midline thalamic nucleus reuniens (RE) has a role in coordinating slow-wave activity between the cortex and hippocampus (HPC). During rapid eye movement (REM) sleep, ponto-geniculo-occipital (PGO) wave activity possibly generated in the pedunculopontine nucleus (PPN) is linked to theta oscillations in the HPC. Hippocampal parvalbumin-expressing interneurons (PVIs) are important for theta-band activity and are strongly recruited during ripple oscillations.

Ach = acetylcholine; CA_1 = cornu ammonis 1; CA_3 = cornu ammonis 3; LGB = lateral geniculate body.

is not fully defined.[23] Alterations in the thalamic medial dorsal nucleus have been reported in the prion disease fatal familial insomnia. CASE 1-1 describes sleep disturbance in another prion disorder, Creutzfeldt-Jakob disease. Both fatal familial insomnia and the contactin-associated protein 2 antibody–mediated Morvan syndrome are associated with motor (oneiric stupor) and autonomic overactivation, a pattern named agrypnia excitata.[24,25]

Synchronized rhythmic activity between the prefrontal cortex and hippocampus is important for mnemonic processes. The midline thalamic nucleus reuniens has a role in coordinating slow-wave activity between the prefrontal cortex and hippocampus.[28]

Strong evidence implicates the claustrum, a subcortical structure located between the insula and putamen, as the coordinator of slow-wave sleep. Neuronal activity in the claustrum is highest during slow-wave sleep. Claustrum neurons project over large cortical regions, which allows them to control sleep slow oscillations.[29,30] The claustrum receives projections from the thalamic medial dorsal nucleus, basolateral amygdala, and serotonergic neurons of the dorsal raphe nucleus.

Genome-wide analyses involving genes expressed in specific neurons from the claustrum and striatum suggest a genetic component of insomnia. The link between insomnia and a disruption of claustrum circuitry suggests an additional role for this area in sleep initiation.[31]

CIRCADIAN RHYTHMS, SLEEP, AND METABOLISM

The 24-hour circadian rhythm is sustained by the translational-transcriptional feedback loop of the molecular clock, which is present in most cells including those in the circadian pacemaker known as the suprachiasmatic nucleus of the hypothalamus. The suprachiasmatic nucleus, situated above the optic chiasm, receives light input via the retinohypothalamic tract to entrain circadian timing to environmental light-dark cycles.[18]

Melanopsin is a retinal pigment that is expressed in intrinsically photosensitive retinal ganglion cells. These cells detect environmental brightness; when depolarized, they utilize the excitatory amino acid glutamate and the cotransmitter pituitary adenylate cyclase-activating polypeptide. Axons of intrinsically photosensitive retinal ganglion cells exit the retina via the retinohypothalamic tract. Targets of the retinohypothalamic tract include the suprachiasmatic nucleus, habenula, subparaventricular zone, VLPO nucleus, and intergeniculate leaflet of the lateral geniculate nucleus. These multiple targets provide diverse retina-brain pathways for the effect of light on mood and circadian rhythms[32,33] (FIGURE 1-4).

Suprachiasmatic nucleus neurons express GABA and different types of neuropeptides. GABA appears to modulate circadian output from the suprachiasmatic nucleus, but the precise action of GABA in the suprachiasmatic nucleus is not yet known.[34] Melatonin is the main source of timing clues for the suprachiasmatic nucleus. Melatonin exerts action via two receptors: MT-1 and MT-2. Melatonin binding to the MT-1 receptor reduces the suprachiasmatic nucleus alerting signal (CASE 1-2). Currently available nonselective melatonin receptor agonists include tasimelteon and ramelteon, along with agomelatine, the first melatoninergic antidepressant. The suprachiasmatic nucleus projects to the dorsomedial hypothalamic nucleus, which is reciprocally connected with the lateral hypothalamic orexin (hypocretin) system.[35] The suprachiasmatic

KEY POINTS

- The basolateral amygdala contributes to the slow-wave sleep–to–REM sleep transition and also sends extensive γ-aminobutyric acid–mediated (GABA-ergic) projections to brainstem regions that promote waking muscle tone and may trigger cataplexy in response to emotions in patients with narcolepsy.
- Claustrum neurons project over large cortical regions, which allows them to influence sleep slow oscillations.
- The habenula receives information from the melanopsin-containing intrinsically photosensitive retinal ganglion cells, potentially representing an extended circadian system.

CASE 1-1

A 48-year-old woman was referred to the sleep clinic for a 1-year history of insomnia (difficulty with sleep initiation and maintenance), decreased dreaming, occasional dream enactment behaviors, and cognitive decline. She had no history of snoring, parasomnias, restless legs syndrome, alcohol use, or psychotropic substance use. Actigraphy recording for 10 days showed a sleep duration of 4 hours with no suggestion of circadian dysrhythmia.

Trials of clonazepam, zolpidem, and eszopiclone were unsuccessful and poorly tolerated due to incoordination. A few months after the development of insomnia, she experienced muscle spasms, irritability, and gait impairment. Physical examination revealed mild hypomimia, bilateral hyperreflexia in the lower extremities, myoclonic jerks, and ataxic gait. A polysomnogram revealed no sleep-disordered breathing but incidentally showed rapid eye movement (REM) sleep without atonia. CSF analysis revealed a nonspecific elevation of 14-3-3 protein. Brain MRI demonstrated diffusion-weighted hyperintensities predominantly affecting the basal ganglia and thalami (FIGURE 1-3). Trazodone 50 mg was administered and titrated to 300 mg over a period of 3 weeks. Upon follow-up, the patient noted benefit with a self-reported sleep duration of 7 hours. Her insomnia severity index score was 7, indicating no clinically significant insomnia. Her neurologic findings progressively declined, and she died 10 months later. Autopsy was confirmatory for Creutzfeldt-Jakob disease, with no co-occurrence of Lewy body pathology.

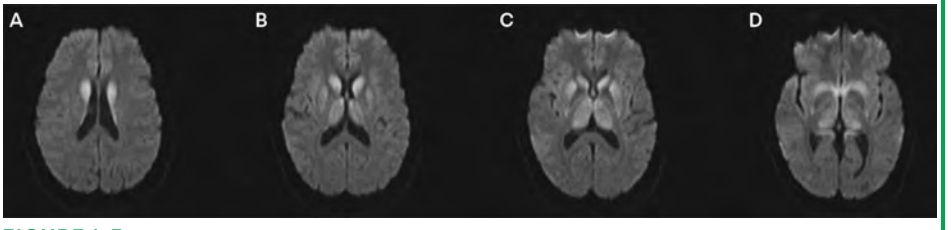

FIGURE 1-3
Axial diffusion-weighted MRI of the patient in CASE 1-1. The imaging demonstrates restricted diffusion in the basal ganglia and thalami bilaterally. *A* represents the most cephalad segment and *D* the most caudal segment.

COMMENT

This case illustrates trazodone-responsive severe insomnia as an initial nonmotor manifestation of the most common human prion disease, sporadic Creutzfeldt-Jakob disease. Sleep alterations in Creutzfeldt-Jakob disease are present in 90% of individuals at the time of presentation, with insomnia being the most prevalent sleep alteration.[26] The prominent basal ganglia involvement seen on imaging in people with Creutzfeldt-Jakob disease supports the potential role of basal ganglia in sleep-promoting mechanisms (FIGURE 1-3).

No evidence advocates for the use of any specific pharmacologic agent for the treatment of insomnia linked to prion diseases in humans. Low-dose trazodone was effective in this case; however, the mechanism behind this relationship is not clear.[27]

nucleus also sends inhibitory projections to the paraventricular hypothalamic nucleus, which controls melatonin secretion via the sympathetic system. The paraventricular hypothalamic nucleus has projections to the upper thoracic intermediolateral cell column via the medial forebrain bundle and to preganglionic sympathetic fibers to the superior cervical ganglion. Postganglionic sympathetic fibers from the superior cervical ganglion interact with β-adrenergic receptors in the pineal gland to release melatonin. Lesions of the paraventricular hypothalamic nucleus abolish the nocturnal rise in pineal melatonin.[36] In contrast, the retinal melanopsin projections to the suprachiasmatic nucleus participate in the suppression of melatonin secretion.

The circadian clock genes are directly coupled to glucose and fatty acid metabolism and regulate processes influencing mitochondrial physiology. Dynamin-related protein 1 directs mitochondrial fusion and fission processes that are essential for oxidative phosphorylation and adenosine 5′-triphosphate production. Dynamin-related protein 1 is phosphorylated in a circadian fashion.[38,39]

Besides light, the circadian clock can be entrained by feeding-related cues. The extra-suprachiasmatic nucleus circadian oscillator, the habenula, interacts with the lateral hypothalamic area and is potentially involved in the regulation of feeding behavior.[40]

Circadian misalignment in mice induced by "wrong-time feeding" causes a shift toward hepatic lipid synthesis and deregulation of hepatocarcinogenic genes.[41] Conversely, restricting meals to a normal active time (daytime in humans) reduces hepatic steatosis by 50% in mice.[42-44] Gluconeogenesis and glycogenolysis are promoted in the liver during sleep (fasting time). Consequently, feeding time (chrononutrition) in accordance with each individual chronotype (the individual variation in the phase of entrainment, classifying individuals into morning or early risers, and evening or night owls) appears to be important for maintaining circadian and metabolic health.

Circadian rhythms and sleep are increasingly seen as important for immune system homeostasis. Immune responses including leukocyte mobilization and trafficking, cytokine release, and T-cell differentiation are mediated in a time-of-day–dependent manner. Sleep disorders such as insomnia and sleep-disordered breathing are also associated with dysregulation of inflammatory processes.[45] The details of the immune responses involved in these processes are beyond the scope of this article.

Circadian rhythm disruption is induced by shift work, excessive nighttime light exposure, and social jet lag (caused by incongruence between the individual chronotype and schedule modifications due to social, school, and occupational demands). As a result, the connection between circadian rhythms, sleep, and immune function has a wide range of implications for public health.[46,47] For more information on the public health implications of circadian rhythm disruption, see the article "Implications of Sleep Health Policy: Daylight Saving and School Start Times," by Karin G. Johnson, MD, FAAN, FAASM, and Beth A. Malow, MD, MS, FAAN,[48] in this issue of *Continuum*.

KEY POINT

● Circadian rhythm disruption is associated with a greater risk of metabolic dysregulation and may also have pathophysiologic effects on psychiatric and neurodegenerative disorders.

SLOW-WAVE SLEEP AND HIPPOCAMPAL ACTIVITY: POTENTIAL FOR MEMORY NETWORK TRANSFERENCE

Although learned material can be consolidated during wakefulness, sleep further ensures the consolidation of memories by impeding incoming sensory

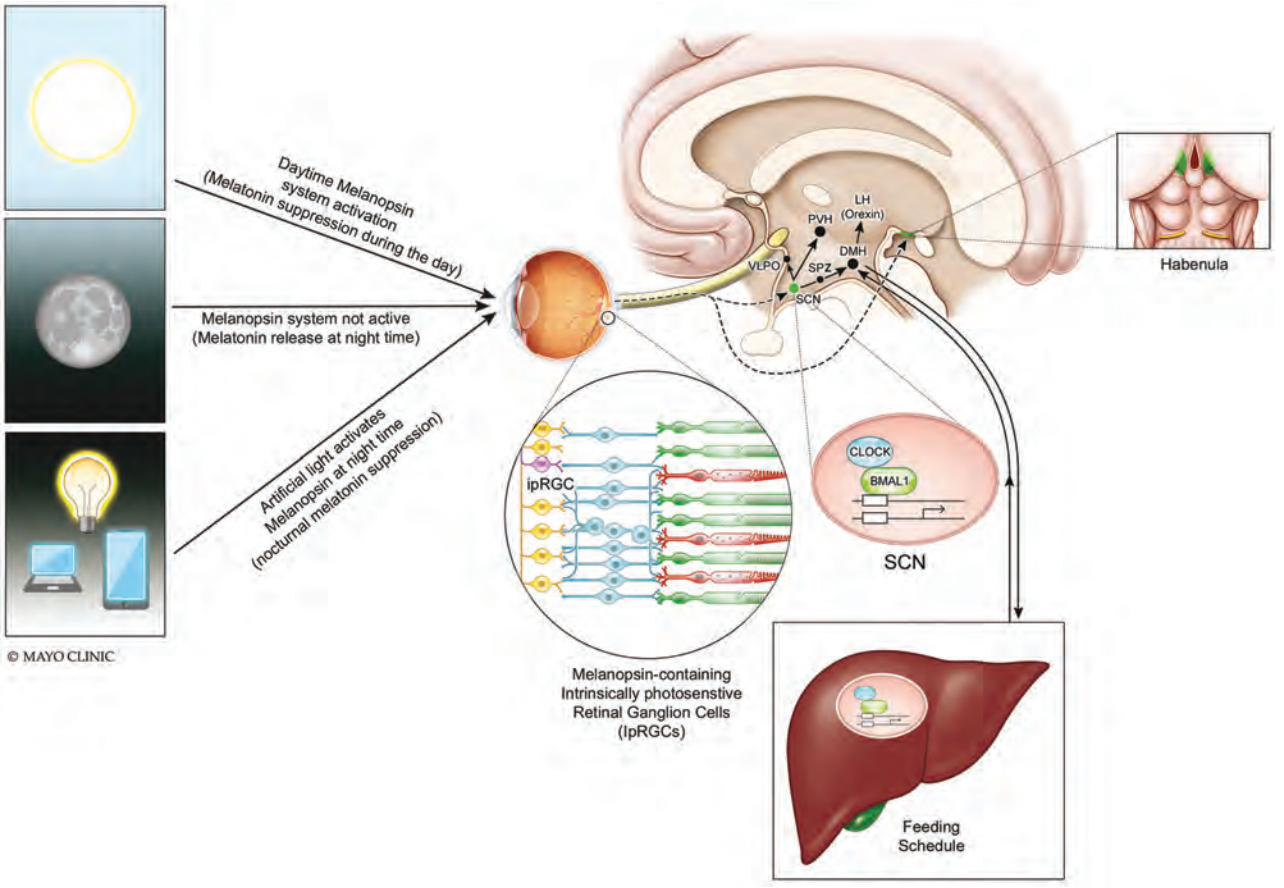

FIGURE 1-4
Simplified representation of the circadian rhythm networks, with only an abbreviated core molecular clock circuitry depicted. Axons of intrinsically photosensitive retinal ganglion cells (ipRGCs) exit the retina via the retinohypothalamic tract (RHT), shown with dotted lines. Some of the targets of the RHT are displayed including the suprachiasmatic nucleus (SCN), habenula (Hb), subparaventricular zone (SPZ), and ventrolateral preoptic (VLPO) nucleus. Additional SCN projections to the paraventricular hypothalamic nucleus (PVH) and dorsomedial hypothalamic nucleus (DMH) reciprocally connected with the lateral hypothalamic (LH) orexin (hypocretin) system are shown. Located lateral to the pineal gland, another oscillator is the Hb (*small green ovals*). The Hb is under local circadian control and receives direct input from the photoreceptors.

interferences (novel signals) that are more likely to occur during wakefulness (FIGURE 1-2). During slow-wave sleep, reduced acetylcholine input to the hippocampus allows autoexcitation from the pyramidal neurons in the CA3 region of the hippocampus to produce local field potentials, known as sharp negative waves, followed by fast (150 Hz to 200 Hz) ripples. Deficits in this activity are seen in both amyloid pathology and animal models of neuropsychiatric disease.[49]

In contrast, high levels of acetylcholine during wakefulness and REM sleep are associated with theta oscillations in the hippocampus, propagating to phase-locked cerebellar oscillations.[50]

Based on the physiologic progression of sleep architecture where slow-wave sleep precedes REM sleep, the contribution of each sleep stage to memory consolidation appears to be sequential. This hypothesis proposes that memories

are first replayed during slow-wave sleep and then integrated into existing networks during REM sleep.[51,52]

NETWORKS OF WAKEFULNESS

The brainstem and hypothalamic regions have different groups of well-characterized monoaminergic, glutamatergic, and cholinergic arousal neurons which are functional components of the ascending arousal system. The ascending arousal system is divided into two branches: a dorsal pathway projecting to the thalamus, and a ventral pathway that reaches the hypothalamus and the basal forebrain. The relevant anatomical structures include the cholinergic basal forebrain, glutamatergic parabrachial nucleus (involved in arousal response to hypercarbia or hypoxia), and pedunculopontine nucleus. Monoaminergic arousal inputs arise from the locus coeruleus, which provides norepinephrine to the cortex, serotoninergic dorsal raphe, dopaminergic neurons of the ventral tegmental area, and ventrolateral periaqueductal gray. The hypothalamic arousal groups include the histaminergic tuberomammillary nucleus and the orexin (hypocretin)-containing lateral hypothalamus.

The pedunculopontine nucleus, situated in the upper pons, modulates wakefulness and REM sleep. The pedunculopontine nucleus receives inputs from wake-active orexin (hypocretin) neurons of the posterior lateral hypothalamus

CASE 1-2

A 5-year-old boy with a history of infantile hypotonia presented to the sleep clinic with developmental and speech delay, daytime hypersomnia, temper tantrums with self-injury (skin picking), and sleep disturbance. Family life was impacted by the daytime behaviors and frequent prolonged nocturnal awakenings. He was initially diagnosed with advanced sleep phase syndrome. On examination, the child was noted to have facial dysmorphism and depressed muscle stretch reflexes.

Genetic testing established the diagnosis of Smith-Magenis syndrome. Treatment was initiated with acebutolol in the morning and an evening dose of melatonin. After 2 weeks, he experienced a significant improvement in his tantrums and picking and an increased ability to concentrate, as well as a reduction in night awakenings and increased sleep duration.

COMMENT

Smith-Magenissyndrome is a circadian syndrome caused by interstitial deletions of chromosome 17p11.2, which affects the retinoic acid induced 1 (*RAI1*) gene. *RAI1* is expressed in many tissues, acting as a transcriptional regulator.[37] Under physiologic conditions, melatonin release is driven by darkness and impeded by light exposure. Children with Smith-Magenis syndrome have paradoxical release of melatonin with diurnal rather than nocturnal secretion. The combination of morning β1-adrenergic antagonist and evening melatonin administration restores circadian melatonin rhythm, enhances sleep, and decreases behavioral disturbances. This case illustrates how the disruption of the circadian rhythm of melatonin in Smith-Magenis syndrome can be treated by pharmacologic suppression of inappropriate diurnal melatonin secretion and augmentation of melatonin activity at night.

KEY POINTS

- Coordinating activity between parahippocampal ripples and widespread sleep spindles supports the concept of a hippocampal-neocortex coupling and information transfer during sleep.
- The orexin (hypocretin) system is involved in both the promotion of wakefulness and the regulation of feeding, motivation, endocrine, and autonomic activities. Narcolepsy type 1 is a consequence of orexin (hypocretin) system dysfunction.

and histaminergic neurons of the tuberomammillary nucleus. Pedunculopontine nucleus neurons exhibit gamma frequencies during wake and REM sleep, but not during slow-wave sleep. The pedunculopontine nucleus' connectivity with the intralaminar parafascicular nucleus of the thalamus is critical for cortical arousal. This interaction between the pedunculopontine nucleus and the parafascicular nucleus of the thalamus propagates synchronized fast gamma oscillations (30 Hz to 60 Hz) to the white matter networks (an anatomical substrate crucial for alertness) and cortical columns.[53] The pedunculopontine nucleus maintains gamma activity by two types of voltage-dependent calcium channels: the P/Q-type channel during wakefulness, and the N-type channel during REM sleep (FIGURE 1-5[54]).

Dopaminergic projections from the ventral tegmental area to the nucleus accumbens promote the transition from sleep to wakefulness. Projections from ventral tegmental area dopaminergic neurons to the nucleus accumbens may cause arousal through the inhibition of adenosine A2A and dopamine D2–expressing (sleep-promoting) nucleus accumbens neurons, highlighting the strength of the ventral tegmental area–nucleus accumbens connection in supporting arousal.[55]

Eugeroics (wakefulness-promoting agents) increase dopamine levels in the nucleus accumbens and dorsal striatum. Modafinil-induced arousal is blocked in ventral tegmental area–lesioned mice, suggesting that ventral tegmental area dopaminergic neurons are essential for modafinil-induced arousal. An important group of neuropeptides synthesized in the lateral hypothalamic region are the orexins (hypocretins). Orexin (hypocretin) peptides are divided into two isoforms: orexin-A (ORX1 or hypocretin-1) and orexin-B (ORX2 or hypocretin-2). Considered crucial for cortical arousal stabilization, the orexin (hypocretin) system neurons fire rapidly in wakefulness but are silent during slow-wave sleep and REM sleep. There is higher orexin (hypocretin) expression during the active period in mice, suggesting that orexin (hypocretin) mRNA

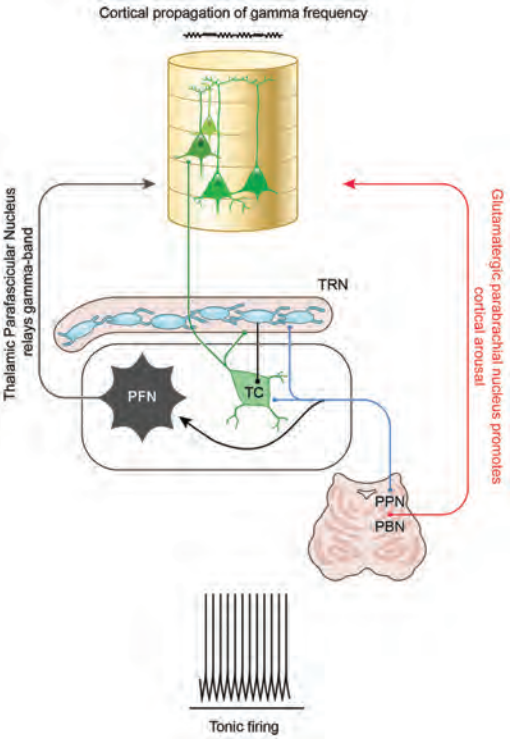

FIGURE 1-5
Pedunculopontine nucleus (PPN) neurons exhibit gamma frequencies during tonic firing of wakefulness. PPN connectivity with the intralaminar parafascicular nucleus of the thalamus (PFN) is critical for cortical arousal. PPN-PFN interaction propagates synchronized fast gamma oscillations. Also depicted is the glutamatergic parabrachial nucleus (PBN) involved in arousal response to hypercarbia or hypoxia.
TC = thalamocortical neuron; TRN = thalamic reticular nucleus. Modified with permission from Benarroch E, 2021.[54] © 2021 Oxford University Press.

levels are under circadian control. The *HCRT* gene is under the influence of the basic helix-loop-helix family member e41 (*BHLHE41*) transcription factor DEC2, which regulates the circadian clock. Humans with *BHLHE41* mutations are short sleepers, and it is not known if their short sleep duration is the consequence of raised orexin (hypocretin) levels.[56-58] The orexin (hypocretin) system is involved in mechanisms of emotional arousal, reward, and short-term regulation of feeding. Narcolepsy type 1 is a consequence of orexin (hypocretin) system dysfunction. The orexin (hypocretin) neurons are influenced by peripheral hormones like ghrelin and leptin, supporting a role between orexin (hypocretin) and metabolism. These mechanisms are mediated by two orexin (hypocretin) receptors with different functions. The ORX1 receptor is associated with motivation and autonomic function and the ORX2 receptor is related to sleep-wake control. The drugs suvorexant, daridorexant, and lemborexant promote sleep by nonselective orexin (hypocretin) receptor antagonism. The bed nuclei of the stria terminalis, a component of the amygdala, facilitate the

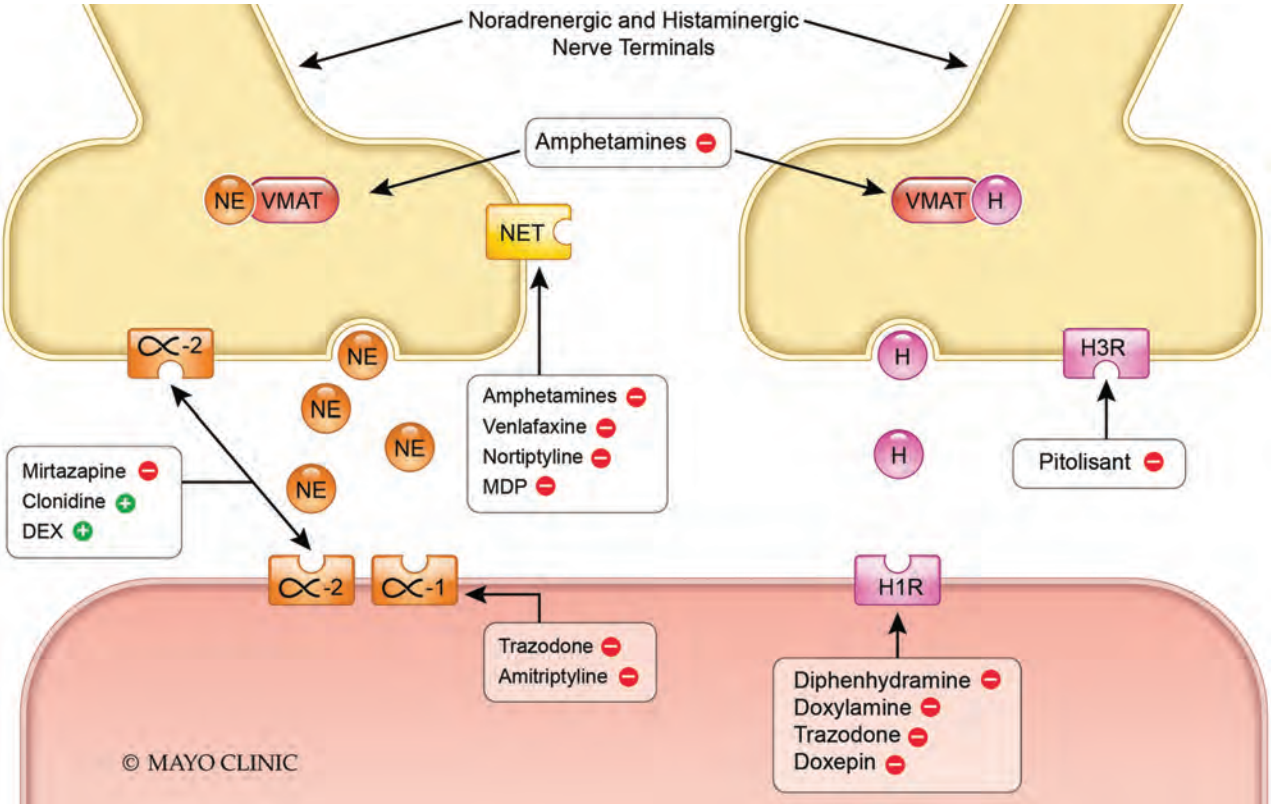

FIGURE 1-6

Mechanisms of action of commonly used medications to treat insomnia and excessive daytime sleepiness. Amphetaminelike stimulants increase wakefulness by blocking catecholamine reuptake and stimulating catecholamine release (ie, noradrenaline and dopamine). Dexmedetomidine is a selective agonist of the α_2-adrenergic receptors with resulting inhibition of the locus ceruleus, which in turn leads to disinhibition of ventrolateral preoptic region firing.

α-1 = α_1-adrenergic receptors; α-2 = α_2-adrenergic receptors; DEX = dexmedetomidine; H = histamine; H1R = histamine-1 receptor; H3R = histamine-3 receptor; MPD = methylphenidate; NE = norepinephrine; NET = norepinephrine transporter; VMAT = vesicular monoamine transporter; – = antagonist or inhibitor; + = agonist.

KEY POINT

● **Although caffeine promotes alertness, the subjective alerting benefit may be at the expense of a reduction of slow-wave sleep duration.**

transition from slow-wave sleep–non-REM sleep to wakefulness and mobilize the orexin (hypocretin) system to sustain wakefulness.[59] The projections of orexin (hypocretin) neurons to the tuberomammillary nucleus, serotonergic neurons in the raphe nuclei and locus ceruleus, cholinergic neurons in the basal forebrain, and dopaminergic neurons in the ventral tegmental area promote consolidated wakefulness.

The tuberomammillary nucleus neurons contain histamine and promote wakefulness by the excitation of H1 receptors. H1 receptor antagonism by drugs like doxepin induces sleep. Presynaptic H3 receptors limit histamine release. Pitolisant, through its H3 receptor antagonism, increases the release of histamine and promotes wakefulness (**FIGURE 1-6**).

Caffeine, the most widely used stimulant, is metabolized via the cytochrome P450 (CYP) isozyme CYP1A2 (subsequent metabolites include paraxanthine, theophylline, and theobromine). Interindividual variation in CYP1A2 activity exists, and individuals with CYP1A2 polymorphisms resulting in "slow" metabolism are likely to be less tolerant to high doses of caffeine.[60,61] Additionally, differences in adenosine receptor genes also contribute to individual caffeine sensitivity.[62] Due to adenosine antagonism, caffeine can attenuate homeostatic sleep pressure, reduce slow-wave sleep duration, and affect circadian-regulated REM sleep.[63-66]

CONCLUSION

Neurobiology will continue to enhance our understanding of the circuitry underlying sleep and wakefulness. The identification of neuronal assemblies and networks as potential targets for sleep neuromodulation is promising for the advancement of care for people with sleep disorders.

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Clinical Evaluation of the Sleepy and Sleepless Patient

By Samuel A. Taylor Jr, MD, MS

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **This article addresses the approach to the evaluation of patients who present to a neurologist with excessive daytime sleepiness or difficulty sleeping.**

LATEST DEVELOPMENTS: **Greater emphasis on the importance of sleep reflects the growing scientific understanding that sleep is critical to overall health and well-being. Consumer sleep technologies, which measure parameters related to sleep, may provide insight into an individual's sleep-related symptoms and tendencies and have a role in patient-centered sleep evaluation when used within an appropriate clinical context.**

ESSENTIAL POINTS: **A thorough review of a patient's history and physical examination findings are important components of the assessment and management of their sleep-related symptoms. An understanding of how the clinical context relates to the categorization of sleep disorders can impact a patient's symptoms, comorbid neurologic disorders, and overall well-being. Many neurologic conditions are strongly associated with sleep disturbance, risk factors for the development of a sleep disorder, or both. Therefore, it is critical for neurologists to be familiar and comfortable with taking a focused sleep history. Modalities such as in-laboratory polysomnography, home sleep apnea testing, multiple sleep latency testing, and actigraphy, as well as contextualized and prudent use of data obtained from consumer sleep technologies, can be helpful in appropriately selected patients. Mindful integration of these objective data facilitates the diagnosis and management of sleep disorders.**

INTRODUCTION

Excessive sleepiness and the inability to sleep are commonly encountered neurologic symptoms that may occur in isolation or in combination with one another. These disturbances of wakefulness and sleep may represent a primary sleep-wake disorder, be part of a separate neurologic disease or syndrome, or be a side effect of some other treatment. Identification of the symptom time course (eg, paroxysmal versus progressive, acute versus chronic) and familiarity with the diagnostic categories of sleep disorders provides a framework for differential diagnosis to guide diagnostic and therapeutic care plans.

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RELATIONSHIP DISCLOSURE:
Dr Taylor reports no disclosure.

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Dr Taylor reports no disclosure.

KEY POINTS

- Familiarity with the main categories of sleep-wake disorders provides a framework for differential diagnosis to guide diagnostic and therapeutic care plans.
- The evaluation of excessive daytime sleepiness requires direct inquiry about the presence of associated sleep paralysis, sleep-related hallucinations, cataplexy, and disrupted or fragmented sleep.

Diagnostic data may be gathered from several sources including, but not limited to, objective neurophysiologic testing, patient-reported data (eg, sleep diaries, survey instruments), and consumer sleep technologies. These modalities vary in measurement frequency, specificity, and sensitivity. Polysomnography is not required for the diagnosis of every sleep-wake disorder but has a role in the evaluation and longitudinal management of specific disease processes. Other in-laboratory and home-based procedures are supported by evidence-based guidelines for specified sleep-wake disorders. The general population is increasingly collecting data through consumer wearable devices, and neurologists are seeing more patients with these devices, although differences across devices and the proprietary nature of their algorithms make it difficult to develop evidence-based guidelines on the use of each available consumer technology. Consumer sleep technologies enhance patients' engagement with their health and help to better define behavioral and, to a lesser extent, physiologic trends. At present, however, data from consumer sleep technologies cannot be used to confirm the diagnosis of a sleep disorder. Awareness of the strengths and limitations of the multitude of sleep-related data sources is akin to the familiarity that neurologists must also have with other evaluation tools (eg, reflex hammer, tuning fork) used in clinical practice.

SLEEP HISTORY

A detailed sleep history is necessary to place a patient's sleep concerns in context with their neurologic and medical history.

Clinical History

A general framework for obtaining the clinical history, along with an awareness of the six major categories of sleep disorders, informs the clinical approach to each patient.[1,2] The six major categories of sleep disorders are:

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

SLEEP HISTORY. The approach to the sleep history should be consistent for all individuals, whether the chief concern is excessive sleepiness, inability to sleep, or another sleep-related symptom. Additional history from a bed partner, roommate, or caregiver can provide insight about the individual's sleep-related symptoms and behaviors.

Discussion about sleep quality can elucidate characteristics of the sleep disturbance or concern. Questions such as "How would you describe your sleep quality?" or "Do you feel restored from your sleep?" can help identify the primary sleep concern. Assessment of sleep duration and continuity with questions such as "How much sleep do you get in a 24-hour period?" and "Do you awaken frequently during sleep?" provide important historical details. Timing of sleep can be discussed with questions such as "What time do you go to bed?", "How long does it take you to fall asleep?", "What time do you wake up?", and

"What time do you rise (get out of bed) to begin your day?" These historical details establish a framework from which formulation emerges to inform the assessment and differential diagnosis, leading to a specific sleep disorder classification.[1,2]

The sleep history should also include questions about sleep-disordered breathing (eg, snoring, witnessed apneas, choking or gasping during sleep, morning headaches), symptoms of sleep-related movement disorders (eg, bruxism, restless legs syndrome [RLS]), clinical evidence of parasomnias (eg, sleepwalking, sleep talking, dream enactment behavior), and daytime sequelae. Information about sleeping position and history of nasal or other upper airway surgeries can be pertinent for those with sleep-disordered breathing concerns. Collateral history can provide additional context about the individual's sleep-related routines, behaviors, and symptoms (CASE 2-1). As is done with the general neurologic history, the sleep history should include a discussion about prior and current medications, supplements, and behavioral measures taken to alleviate the presenting concerns.

DAYTIME SYMPTOMS. For patients who present with excessive daytime sleepiness, contextual details are critical to gauge the severity and potential safety risks. Specific questions should include driving safety, academic and occupational performance, and interpersonal relationships. Individuals may use a variety of terms such as tiredness, fatigue, lethargy, and sleepiness to describe the symptom that affects their level of daytime alertness and energy level. The evaluation of excessive daytime sleepiness requires direct inquiry about the presence of associated sleep paralysis, sleep-related hallucinations (hypnagogic: at sleep onset; hypnopompic: at sleep offset), cataplexy (transient loss of muscle tone induced by abrupt emotion, such as laughter), and disrupted or fragmented sleep.

Insomnia and, more generally, sleeplessness, are among the most common sleep-related concerns. In the United States, approximately 30% of people

CASE 2-1

A 54-year-old man with a history of obesity and hypertension presented at the insistence of his wife, who noted that he had a long history of snoring and now had observable apneas during sleep. He was unaware of the described symptoms but noted that his sleep quality had worsened with gradual weight gain over the past few years. On further discussion, he endorsed multiple awakenings for nocturia, frequent tossing and turning, and waking with severe morning headaches that resolved within 30 minutes of waking. He felt intermittently sleepy during the day, especially when sitting quietly at his desk, which affected his work performance. He had occasional difficulty staying awake on the commute home when stopped for a prolonged period at a stoplight.

COMMENT

This case exemplifies symptoms suggestive of obstructive sleep apnea and thus merits further diagnostic evaluation with either a home sleep apnea test or in-laboratory polysomnography. The case also illustrates the importance of gathering information from a collateral historian whenever possible in the evaluation of sleep-wake disorders.

report some degree of clinically significant insomnia at some point in their life, and approximately 10% will develop chronic insomnia disorder.[1] The prevalence of insomnia is even higher in individuals with Parkinson disease, multiple sclerosis, or stroke.[3] Insomnia can impair quality of life as well as school and work performance. Insomnia can exist as a distinct disorder or may be a symptom of another primary sleep disorder such as obstructive sleep apnea (OSA). Adults are recommended to get at least 7 hours of sleep nightly[4]; less total sleep time on a regular basis may cause chronic partial sleep deprivation that could result in daytime sleepiness. The three-process (3-P) model of chronic insomnia disorder is a conceptual framework introduced by Arthur Spielman and colleagues[5] that describes the evolution of a patient's insomnia based upon **p**redisposing, **p**recipitating, and **p**erpetuating factors and tendencies.

Insomnia generally manifests in four forms:

- **Difficulty initiating sleep**
- **Difficulty maintaining sleep**
- **Early morning awakenings**
- **Overall poor sleep quality despite adequate time allowed to sleep, which is not otherwise associated with or explained by any medical condition, another primary sleep disorder, or medication or substance use**

Critical details about nocturnal awakenings include timing, duration, and presumed causes (eg, ambient noise, need to urinate, pain) of each awakening, and measures taken to fall back asleep after each awakening. This information helps to identify difficulties with sleep initiation, maintenance, or both and provides a general idea of average total sleep time on a regular basis. Discussion about the sleeping environment and sleep-related habits provides useful insight about potential perpetuating factors of the individual's insomnia.

The time course of the current bout of insomnia (ie, acute, subacute, or chronic) and the presence of a personal or family history of insomnia highlights risk factors for insomnia disorder and can guide discussions about potential treatment options and anticipated treatment response.

MEDICAL HISTORY. A review of the patient's medical history identifies comorbid conditions (eg, anxiety, depression, posttraumatic stress disorder) that may influence insomnia and its treatment. Additionally, individuals with neurodegenerative disorders such as Parkinson disease and dementia with Lewy bodies more commonly experience recalcitrant or progressive insomnia.[3] Optimization of pain control is central to the management of insomnia associated with chronic pain; collaboration between the neurologist and the patient's other clinicians may be required.

The medical history may help broaden the differential diagnosis and assess the risk for sleep disorders. For instance, hypertension and cardiovascular or neurovascular disease are associated with an increased risk of OSA. A history of heart failure (especially with reduced ejection fraction), atrial fibrillation, and central neurologic disorders such as stroke and multiple sclerosis can each be associated with central sleep apnea. Neuromuscular disorders, especially those associated with respiratory muscle dysfunction, may confer a predisposition

to hypoventilatory disorders. Individuals with known α-synucleinopathy may develop rapid eye movement (REM) sleep behavior disorder (RBD). In addition, RBD may be a prodromal biomarker for later development of α-synucleinopathies (eg, Parkinson disease, dementia with Lewy bodies, multiple system atrophy).[1]

MEDICATION USE. A detailed medication history is also important to contextualize the patient's sleep-related symptoms and inform future management decisions. A detailed medication history, including over-the-counter medications and herbal supplements and the time course over which they were used, can yield insight about hypersomnolence and insomnia. For example, many antiseizure medications are associated with some degree of hypersomnolence, especially when first initiated, and particularly in an acute setting. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants may contribute to hypersomnolence, RBD, or RLS. Benzodiazepines, dopamine agonists, and opioid analgesics can cause daytime sleepiness, while stimulant medications and corticosteroid medications may increase the risk for insomnia.

SOCIAL AND FAMILY HISTORY. A detailed social history may also elucidate other etiologies of sleep disturbance. Knowledge of the patient's occupation, work hours, and distance and duration of commute informs risk stratification and counseling about the avoidance of drowsy or impaired driving. In fact, some transportation industries include OSA screening as part of standard operating procedures. Discussion about substance use may help identify contributors of hypersomnolence or other sleep disturbances. Nicotine is a stimulant that can increase the likelihood of insomnia in some people.

Assessment of family history is also important in the evaluation of sleep disorders. Non-REM parasomnias of childhood, intrinsic circadian rhythm sleep-wake disorders, narcolepsy, and RLS can have hereditary components. Genetic underpinnings of craniofacial anatomy can influence the likelihood of OSA development. The rare disorder known as fatal familial insomnia also has a genetic influence.

Physical Examination

A focused physical examination can be invaluable in the assessment of sleep disorders. Cardiopulmonary and head and neck examinations are particularly important when evaluating for the possibility of a sleep-related breathing disorder. Individuals with a body mass index greater than or equal to 40 kg/m^2 and a serum bicarbonate greater than 27 mmol/L are at increased risk of obesity hypoventilation syndrome as well as OSA.[5] Anatomic risk factors for sleep-related breathing disorders include micrognathia, retrognathia, macroglossia (evidenced by lateral scalloping of the tongue), a high-arched and narrow hard palate, and overjet (horizontal difference between the upper and lower teeth) (CASE 2-2). A neck circumference greater than 43 cm (17 in) in men and 38 cm (15 in) in women confers an increased risk of OSA.[1] The Mallampati classification, which was developed to gauge the complexity of intubation and airway management during sedation or anesthesia, describes the patency of the oral airway via visualization of the oral cavity with the tongue protruded and no phonation (FIGURE 2-1[6]). Mallampati classes I and II represent greater oral airway patency, with more structures readily visualized. Mallampati classes III and IV

KEY POINTS

- Understanding the 3-P model of insomnia (predisposing, precipitating, and perpetuating factors) is important to both contextualize the patient's sleeplessness and provide a solid foundation for patient education regarding the assessment and care plan.
- The four manifestations of insomnia include difficulty initiating sleep, difficulty maintaining sleep, unintended early morning awakenings, and overall poor sleep quality despite adequate time allowed to sleep.
- Individuals with neurodegenerative disorders such as Parkinson disease and dementia with Lewy bodies more commonly experience recalcitrant or progressive insomnia.
- Non–rapid eye movement (non-REM) parasomnias of childhood, intrinsic circadian rhythm sleep-wake disorders, narcolepsy, and restless legs syndrome can have hereditary components.
- The Mallampati system, developed to assess the complexity of intubation and airway management during sedation or anesthesia, describes various levels of oral airway patency and is used stratify the risk of sleep-disordered breathing.

represent a higher degree of upper airway crowding, which portends an increased risk for obstructive sleep-related breathing disorders such as OSA.

A detailed neurologic examination is important for specific patient populations. Patients with distal polyneuropathy may have comorbid RLS. In the case of RBD, a detailed neurologic examination is necessary to evaluate for signs of neurodegenerative disease (eg, increased tone, rigidity, gait disturbance, bradykinesia, cognitive deficits, frontal release signs).

The physical examination of people with insomnia is frequently unremarkable, although clinicians should remain vigilant for signs of comorbid medical, neurologic, or mental health conditions which might predispose to or precipitate insomnia.

Subjective Rating Scales and Sleep Diaries

The Epworth Sleepiness Scale (FIGURE 2-2[7]) is one of the most widely used subjective assessment tools to gauge excessive daytime sleepiness.[7] This tool assesses tendencies toward sleepiness over the past several weeks by numerically ranking the likelihood of dozing during eight different scenarios. Each scenario is scored between 0 (no likelihood of dozing) and 3 (high likelihood of dozing), with a total score range from 0 to 24. A score above 10 suggests excessive daytime sleepiness in the general adult population.[8] A pediatric version of this scale includes modifications such as including questions about the tendency to doze while playing video games instead of while driving. The Epworth Sleepiness Scale is useful for following sleepiness (and treatment response) in the same individual over time, but it is not used to compare levels of sleepiness between individuals.[9]

Validated clinical survey instruments such as the Pittsburgh Sleep Quality Index or Insomnia Severity Index may help clarify the features and overall

CASE 2-2

A 45-year-old woman with relapsing-remitting multiple sclerosis and moderate asthma presented with persistent daytime fatigue despite a nightly total sleep time of 8 hours. She was diagnosed with multiple sclerosis 20 years prior, had been on disease-modifying monotherapy and in stable remission for over 10 years, and had experienced no exacerbations in the past 5 years. However, her daytime fatigue had persistently worsened without appreciable change in her sleep, diet, or exercise habits. She occasionally snored, particularly after a long or physically challenging day. She did not have a bed partner so was unsure if she had apneas during sleep. Physical examination showed a neck circumference of 41 cm (16 in) and a narrow, high-arched hard palate.

COMMENT

This case presents an example of two conditions (multiple sclerosis and possible obstructive sleep apnea [OSA]) that can have an overlapping symptom of fatigue and can coexist in the same individual. Diagnosis and treatment of OSA can improve quality of life and daytime fatigue for people with multiple sclerosis. An in-laboratory polysomnogram should be pursued to evaluate for OSA.

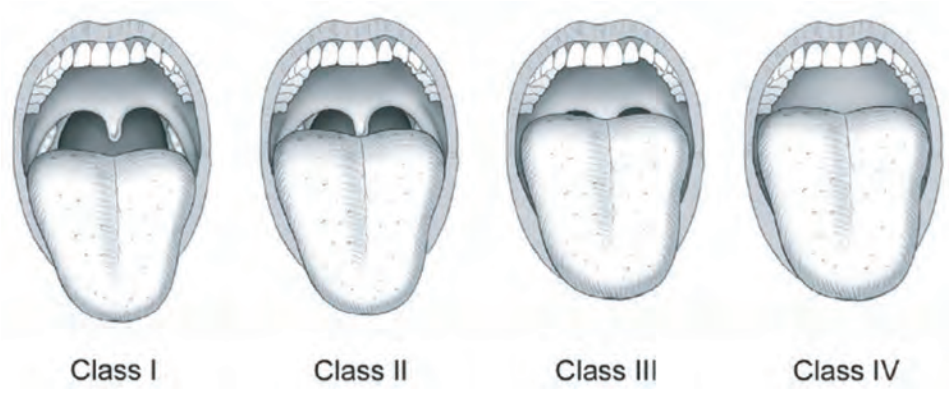

FIGURE 2-1
Mallampati classification. Although initially developed to predict intubation difficulty, the classification was also found to correlate with the risk of obstructive sleep apnea. Class I: the soft and hard palate, uvula, and tonsillar pillars can be seen. Class II: all structures except the tonsillar pillars can be seen. Class III: only the soft and hard palate and the base of the uvula can be seen. Class IV: only the hard palate can be seen.
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severity of insomnia and may help assess treatment response over time.[10] Other useful scales include the STOP-BANG scale for OSA risk stratification (TABLE 2-1[11]) and the International Restless Legs Syndrome Study Group RLS severity rating scale.[12,13]

Sleep diaries are not clinical rating scales, but rather tools that individuals can use to self-record their estimated bedtime, number of awakenings, wake time, and naps. Sleep diaries are often maintained for 7 to 14 days. These diaries may be used clinically to estimate wake, rise, and total sleep times and to provide additional context to the patient's experience of sleep disturbance, hypersomnolence, or insomnia. Sleep diaries can be used in conjunction with actigraphy (see below) to obtain a more objective estimation of sleep-wake times and patterns.

Testing

The gold standard test for the evaluation of sleep is the in-laboratory attended polysomnogram (PSG). As the name signifies, polysomnography includes simultaneous recordings with multiple channels of physiologic data to assess sleep architecture, respiratory parameters, and leg movements, perform limited cardiac monitoring, and observe any abnormal events that might arise from sleep (FIGURE 2-3). The baseline PSG records the following minimum channels: bilateral limited EEG (ie, bilateral frontal, central, and occipital electrode referenced to the bilateral mastoid processes) and electrooculography, chin surface EMG, snore microphone recording, limited ECG, bilateral anterior tibialis surface EMG, nasal pressure transducer, nasal-oral thermistor, chest and abdominal respiratory inductance plethysmography belts, and pulse oximetry. Body position is also scored continuously throughout the study.[14] Carbon dioxide monitoring (end-tidal, transcutaneous, or both) is added for all pediatric studies and can be added for adults in whom sleep-related hypoventilation is suspected. Surface EMG electrodes on the bilateral extensor digitorum may be added to create an extended parasomnia montage for the evaluation of parasomnias, particularly RBD. The addition of pH monitoring or esophageal manometry is

KEY POINTS

- **The Epworth Sleepiness Scale is useful for following sleepiness (and treatment response) in the same individual over time, but it is not used to compare levels of sleepiness between individuals.**
- **The in-laboratory, fully attended polysomnogram is the gold standard test for the evaluation of sleep and identification of most sleep disorders.**

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car or bus, while stopped for a few minutes in traffic	

THANK YOU FOR YOUR COOPERATION

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FIGURE 2-2
Epworth Sleepiness Scale.
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occasionally used to evaluate for reflux-associated sleep-related breathing disorders and more subtle forms of sleep-related breathing disorders, respectively. Polysomnography can also be performed to guide titration of continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) therapy, more advanced forms of noninvasive positive pressure ventilation, or titration of supplemental oxygen with or without positive airway pressure therapy. Because insomnia is a clinical diagnosis, polysomnography is not recommended for the diagnosis or management of insomnia.[15] Polysomnography or home sleep apnea testing may be used to evaluate for suspected comorbid OSA in addition to insomnia.

The STOP-BANG Questionnaire[a] TABLE 2-1

1 Snoring

- Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
  - ◇ Yes/No

2 Tired

- Do you often feel tired, fatigued, or sleepy during the daytime?
  - ◇ Yes/No

3 Observed

- Has anyone observed you stop breathing during your sleep?
  - ◇ Yes/No

4 Blood **p**ressure

- Do you have or are you being treated for high blood pressure?
  - ◇ Yes/No

5 BMI

- BMI more than 35 kg/m^2?
  - ◇ Yes/No

6 Age

- Age more than 50 years old?
  - ◇ Yes/No

7 Neck circumference

- Neck circumference greater than 40 cm (15.75 in)?
  - ◇ Yes/No

8 Gender

- Gender male?
  - ◇ Yes/No

High risk of obstructive sleep apnea: answering yes to three or more items.

Low risk of obstructive sleep apnea: answering yes to fewer than three items.

BMI = body mass index.

[a] Reprinted from Chung F, et al, Anesthesiology.[11] © 2008, American Society of Anesthesiologists.

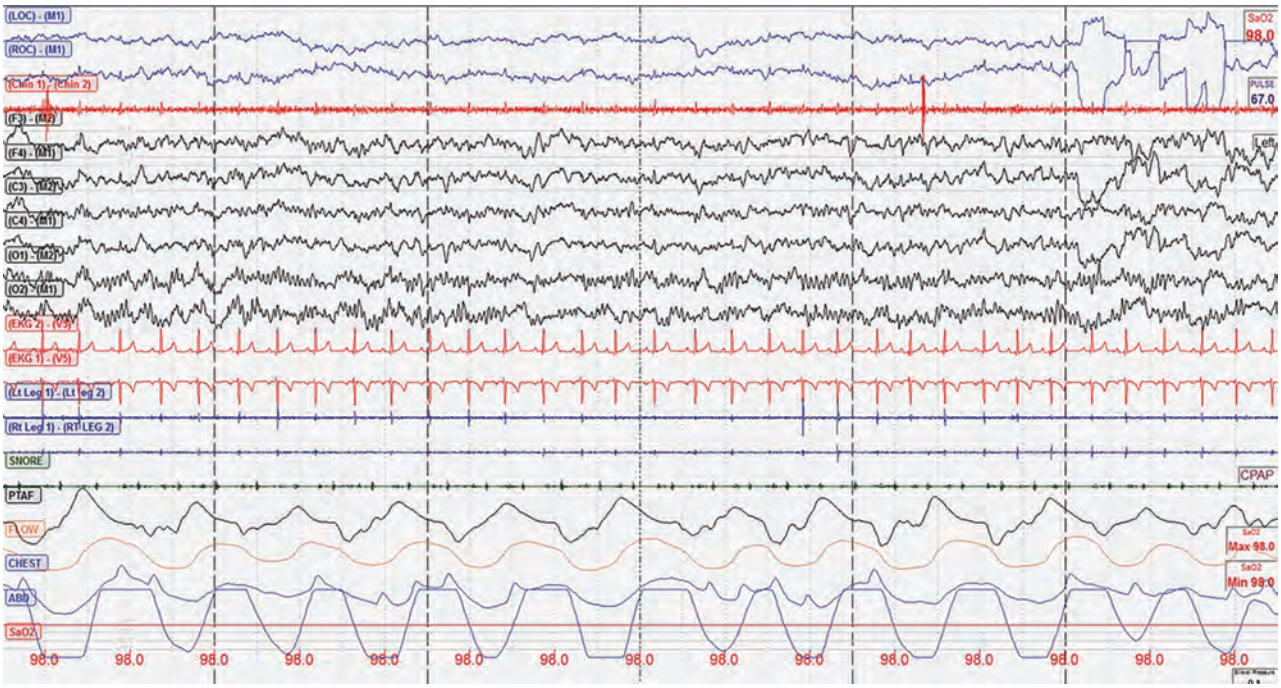

FIGURE 2-3
A standard polysomnographic montage. The typical montage includes: electrooculography (LOC and ROC), EEG of the bilateral frontal (F), central (C), and occipital (O) regions, ECG, bilateral surface EMG of the anterior tibialis, snore microphone signal (SNORE), nasal pressure (PTAF) and nasal-oral thermistor airflow (FLOW) signals, respiratory inductance plethysmography of the chest and abdomen (ie, respiratory effort signals, CHEST and ABD), and pulse oximetry (ie, oxygen saturation, SaO2). Several additional specialized channels may be recorded depending on the suspected sleep related condition, such as bilateral surface EMG of the arm musculature for suspected parasomnia, pH monitoring for suspected gastroesophageal reflux disease–associated sleep-disordered breathing, or esophageal pressure manometry transducer for accurate measurement of quantitative respiratory effort for enhanced diagnosis of sleep related breathing disorders.

The multiple sleep latency test (MSLT) is the gold standard technique for quantifying daytime sleepiness and is used in the diagnostic evaluation of central disorders of hypersomnolence, which include narcolepsy and idiopathic hypersomnia.[1] The MSLT is a limited polysomnographic study that includes only the following channels: bilateral limited EEG, bilateral electrooculography, chin surface EMG, and limited ECG.[14] An overnight PSG performed the night prior to the MSLT allows for the measurement of total sleep time, assessment of sleep architecture, and assessment of other sleep disorders, such as OSA. Current guidelines indicate that the overnight PSG should record at least 6 hours of sleep prior to the MSLT. If a sleep-related breathing disorder or other sleep disorder that might result in excessive daytime sleepiness is detected on the overnight PSG, the MSLT should be deferred until the patient is clinically stable and when treatments for comorbid sleep disorders (eg, OSA) are well established and effective.[16]

The MSLT includes five nap trials, scheduled at different circadian time points throughout the day and each separated by 2 hours. Each nap opportunity is terminated after 20 minutes if the patient does not achieve electrographic sleep.

If the patient achieves electrographic sleep before 20 minutes have passed, the patient is allowed to sleep for an additional 15 minutes. At the conclusion of the five nap opportunities, the mean sleep latency is calculated as the average of the latency to the first epoch (30-second interval) of any stage of electrographic sleep. A mean sleep latency of fewer than 8 minutes in adults indicates excessive daytime sleepiness per comparison with normative data; a mean sleep latency of fewer than 5 minutes indicates severe excessive sleepiness.[16]

A sleep-onset REM period is defined as the onset of REM sleep during any nap trial of the MSLT or within 15 minutes of sleep onset during the PSG. Comprehensive urine drug screens are typically performed on the day of the MSLT to identify any medications that might influence the level of daytime sleepiness. The use of prescription medications such as amphetamines and other stimulants may contribute to false-negative results, and sedating medications such as barbiturates, opiates, anxiolytics, and hypnotic agents may contribute to false-positive results. More extensive or quantitative drug screening panels may be needed in specific clinical scenarios, such as for individuals with chronic pain who routinely take medications that might cause sedation. A 1- to 2-week sleep diary with or without actigraphy should be performed prior to the PSG-MSLT to understand the patient's sleep-wake schedule and duration in the time leading up to the PSG-MSLT. If clinically safe and feasible, medications that might affect wakefulness or confound the study results are typically avoided for approximately 2 weeks or 5 pharmacologic half-lives of the medication to minimize their effects on testing. This approach often applies to antidepressant medications, such as SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs), which are known REM-suppressing medications. However, in some instances it may be most prudent to consult with the prescribing provider before discontinuing any medication with a significant risk of withdrawal or rebound symptoms to ensure safety, facilitate coordination of care, and establish adequate interval monitoring as clinically warranted.

No more than one sleep-onset REM period should be seen on an MSLT in the absence of sleep deprivation or medication effects. A mean sleep latency of fewer than 8 minutes with two or more sleep-onset REM periods is supportive of a diagnosis of narcolepsy if all other causes of hypersomnolence have been excluded. A mean sleep latency of less than 8 minutes with one sleep-onset REM period or less may indicate idiopathic hypersomnia in the appropriate clinical context.

In contrast to the MSLT, the maintenance of wakefulness test is a daytime test intended to assess the patient's ability to remain awake during the testing. A PSG may be performed but is not required prior to the maintenance of wakefulness test, which consists of four 40-minute wake trials that are each separated by 2 hours. The normative reference for mean latency of sleep on the maintenance of wakefulness test is 30.4 plus or minus 11.2 minutes, with a lower limit of normal of 8 minutes. The maintenance of wakefulness test is performed rather infrequently, often in those for whom the possibility of daytime sleepiness may pose a safety threat (eg, individuals who work in the transportation industry).

Actigraphy monitors movement as a surrogate measure of wakefulness to determine periods of activity versus rest. This monitoring is typically performed by a wearable clinical device that measures movement via an accelerometer. Actigraphy can provide a higher degree of objectivity than patient-completed sleep diaries alone when attempting to define the patient's sleep routine and

KEY POINTS

- Diagnostic testing with polysomnography or home sleep apnea testing is not recommended for the diagnosis or management of insomnia.
- The multiple sleep latency test is the current gold standard for quantifying sleepiness and is used in the diagnosis of central disorders of hypersomnolence such as narcolepsy and idiopathic hypersomnia.
- A multiple sleep latency test showing a mean sleep latency of less than 8 minutes with two or more sleep-onset REM periods is supportive of a diagnosis of narcolepsy if all other causes of hypersomnolence have been excluded.
- Medications that might affect wakefulness or confound multiple sleep latency test results are typically avoided for approximately 2 weeks or 5 pharmacological half-lives of the medication to minimize their effects on testing.
- In the proper clinical context, actigraphy can be a useful tool to increase measurement objectivity in the evaluation of insomnia and circadian rhythm sleep-wake disorders.

duration.[17] Thus, actigraphy can be highly useful in the assessment of circadian rhythm sleep-wake disorders and can more objectively evaluate for insufficient sleep prior to MSLT.[17] A practical limitation to the clinical use of actigraphy is the lack of coverage by most insurance companies. Sleep diaries and consumer wearable devices might be able to accomplish similar goals; however, they lack the higher degree of objectivity of clinical actigraphy.[18]

Home sleep apnea testing may be used for the evaluation of OSA in appropriately selected individuals. Home sleep apnea testing involves limited cardiorespiratory monitoring that typically consists of the following channels: nasal pressure transducer, thoracic respiratory inductance plethysmography belt, pulse oximetry, and heart rate. Some home sleep apnea testing devices also include a body position sensor. Home sleep apnea testing does not include EEG monitoring and thus is not used in the diagnostic evaluation of sleep disorders other than OSA.

Consumer Sleep Technologies

As previously mentioned, consumer sleep technologies continue to grow in popularity, variety, and adoption by individuals of all ages. These devices can provide considerable insight into a patient's sleep tendencies and behaviors as well as provide a foundation for optimizing sleep habits. However, the limitations of these devices must always be kept in mind. Many consumer devices work similarly to clinical actigraphy devices but with less precision.[18] Not all commercially available devices are validated for clinical accuracy for measures such as sleep stage identification. As with other tools, the key to unlocking their potential lies in understanding limitations to and opportunities for incorporating these technologies into the management of sleep disorders and sleep quality. As consumer sleep technologies become more sophisticated and achieve a higher degree of validation, they may play an increasing role in the diagnosis and management of sleep disorders and may create opportunities to provide sleep health care to more communities and reduce sleep health disparities.[19-21] Increased access to useful sleep data via consumer sleep technologies may provide deeper insights into the sleep health of underserved populations.[20]

SLEEP SAFETY COUNSELING

Safety counseling is a key component of caring for patients with suspected or confirmed sleep disorders, particularly for disorders associated with excessive sleepiness. Each clinic visit should include counseling to refrain from driving (or any activity that might result in harm to self or others) when feeling sleepy, drowsy, or inattentive. Federal, state, and local laws are increasingly recognizing drowsy driving as another form of impaired driving.[22-24] As drowsiness itself is the first stage of physiologic sleep, it should not be ignored or minimized when performing activities that require alertness and attention. Behaviors such as listening to loud music, turning down the temperature in the vehicle, and rolling down the windows may increase the amount of distraction when someone is feeling sleepy or inattentive.[24] If drowsiness develops while driving, the recommended actions include pulling over as soon as is safely possible and napping for 15 to 20 minutes, using caffeine, or allowing someone else who is alert to drive. In light of these factors, the use of public transportation or a transportation service might also be considered if financially and logistically feasible to optimize safety in the setting of excessive daytime sleepiness.

CONCLUSION

A detailed sleep history and physical examination are keys to accurate and effective evaluation of sleep-related concerns. Many conditions, including neurologic disease, may have a reciprocal relationship with comorbid sleep disorders. Knowledge of the different categories of sleep disorders can help guide the assessment and diagnostic approach for each person.[25] The clinical evaluation of sleep-related concerns is an important first step toward helping all individuals achieve the sufficient, restorative sleep that is integral to overall health and well-being.

USEFUL WEBSITES

AMERICAN ACADEMY OF NEUROLOGY (AAN)–SYNAPSE SLEEP MEDICINE SECTION COMMUNITY
Excellent collegial resource for neurologists engaged in the evaluation and management of sleep disorders.

synapse.aan.com/communities

AMERICAN ACADEMY OF SLEEP MEDICINE (AASM)
Official website of the only professional organization dedicated exclusively to the medical subspecialty of sleep medicine.

aasm.org

AMERICAN SLEEP APNEA ASSOCIATION
Useful patient-centered resource for obstructive sleep apnea.

sleephealth.org

BRAIN BASICS: UNDERSTANDING SLEEP
Useful resource from the National Institute of Neurologic Disorders and Stroke for patient- and caregiver-centered education and support regarding sleep disorders from a neurologic perspective.

ninds.nih.gov/health-information/patient-caregiver-education/brain-basics-understanding-sleep

PITTSBURGH SLEEP QUALITY INDEX
Well-vetted and frequently used survey instrument that assesses overall sleep quality and characteristics.

sleep.pitt.edu/wp-content/uploads/Study_Instruments_Measures/PSQI-Instrument.pdf

RESOURCES: SLEEP AND SLEEP DISORDERS
Useful resource for patients and their families regarding sleep disorder education and support, maintained by the Centers for Disease Control and Prevention.

cdc.gov/sleep/resources.html

SCREENING QUESTIONS–SLEEP HISTORY & PHYSICAL
Useful template to help organize sleep history collection and assessment.

aasm.org/resources/medsleep/(harding)questions.pdf

SLEEP EDUCATION (AASM)
Excellent patient- and caregiver-centered resource for sleep disorders education.

sleepeducation.org

SLEEP FOUNDATION
Helpful educational resource for patients and their families presented in an easily understandable format.

sleepfoundation.org

TWO WEEK SLEEP DIARY
A highly useful tool from the American Academy of Sleep Medicine to more objectively characterize and quantify sleep timing and tendencies.

sleepeducation.org/docs/default-document-library/sleep-diary.pdf

KEY POINTS

- **Home sleep apnea tests are limited cardiorespiratory tests used for the diagnosis of obstructive sleep apnea. These devices are not used to diagnose other sleep disorders.**
- **Consumer sleep technologies may have a role in the clinical evaluation and management of sleep disorders and the optimization of sleep quality, but they are currently not sufficient to establish a diagnosis of any sleep disorder.**
- **If drowsiness develops while driving, the recommended actions include pulling over as soon as is safely possible and napping for 15 to 20 minutes, using caffeine, or allowing someone else who is alert to drive.**

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Central Disorders of Hypersomnolence

By Margaret Blattner, MD, PhD; Kiran Maski, MD, MPH

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **The goals of this article are to describe the clinical approach to and management of patients with central disorders of hypersomnolence, and to understand and differentiate available diagnostic tools.**

LATEST DEVELOPMENTS: **Updated clinical practice guidelines for the treatment of central disorders of hypersomnolence and narcolepsy specifically highlight new treatment options. Approval for a lower-sodium oxybate formulation that contains 92% less sodium than the standard sodium oxybate for the treatment of narcolepsy and idiopathic hypersomnia adds to the number of medications available for these disorders, allowing for a more tailored management of symptoms.**

ESSENTIAL POINTS: **Central disorders of hypersomnolence are characterized by excessive daytime sleepiness that impacts daily functions. These disorders can be differentiated by obtaining a detailed clinical sleep history and by a thoughtful interpretation of sleep diagnostic testing. Tailoring treatment approaches to meet the needs of individuals and accounting for medical and psychiatric comorbidities may improve quality of life.**

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Dr Blattner reports no disclosure. Dr Maski has received personal compensation in the range of $500 to $4999 for serving as a consultant for Alkermes, Eisai Pharmaceuticals, and Zevra Therapeutics and for serving on a scientific advisory or data safety monitoring board for Idorsia Pharmaceuticals, Ltd., and in the range of $5000 to $9999 for serving as a consultant for Harmony
Continued on page 1070

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Blattner and Maski discuss the unlabeled/investigational use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants for the treatment of cataplexy in narcolepsy type 1; armodafinil, clarithromycin, flumazenil, modafinil, and traditional stimulants for the treatment of idiopathic hypersomnia; armodafinil and modafinil for the treatment of hypersomnia; and amantadine, carbamazepine, IV steroids, lithium, phenobarbital, phenytoin, and valproate for the treatment of Kleine-Levin syndrome.

INTRODUCTION

Central disorders of hypersomnolence are primary sleep disorders characterized by profound sleepiness or the excessive need to sleep. In the *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*), these disorders include narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia associated with a psychiatric disorder, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, and insufficient sleep syndrome.[1] The goal of this article is to describe the clinical features, diagnostic evaluation and pitfalls, and management of narcolepsy types 1 and 2, idiopathic hypersomnia, hypersomnia with neurologic diseases (eg, Parkinson disease, traumatic brain injury), and Kleine-Levin syndrome.

CLINICAL APPROACH TO THE SLEEPY PATIENT

The *ICSD-3-TR* defines hypersomnolence as the irrepressible need to sleep or episodes of daytime sleepiness.[1] Patients can have difficulty differentiating between fatigue and sleepiness and may use the terms interchangeably. The clinical description of fatigue may include low energy or feeling tired and is reported across several conditions, whereas sleepiness reflects a propensity to fall

CASE 3-1

A 22-year-old woman presented to the sleep clinic with excessive daytime sleepiness. She had a minor car accident when she fell asleep behind the wheel. She would uncontrollably slump over when she laughed hard and had "smacked" her head while seated at a dining table in this context. She would awaken briefly from sleep at night and had vivid dreams. She took 1- to 2-hour naps every day. Her bedtime was 1 AM and she watched online videos prior to sleep onset. She would awaken with much effort at 6:30 AM on weekdays and slept until 10 AM on weekends. She experienced sleep paralysis when waking in the morning and from naps. She reported no snoring. Her Epworth Sleepiness Scale score was 17 out of 24 (indicating severe daytime sleepiness).

While her symptoms were strongly suggestive of narcolepsy type 1, her physician noted that weekday sleep duration was less than 7 hours at night and this may contribute to daytime sleepiness. A polysomnogram with multiple sleep latency test (MSLT) was ordered and, in the meantime, the physician counseled the patient on sleep hygiene and sufficient sleep time (not using electronic devices 30 minutes before bedtime, maintaining a regular sleep schedule on both weekdays and weekends that allowed for 8 hours of sleep, and limiting daytime naps to less than 1 hour). Her physician requested a 2-week sleep diary prior to testing to assess adherence to the sleep hygiene plan. Despite getting 8 to 9 hours of nighttime sleep, the patient still reported severe sleepiness. The polysomnogram with MSLT showed a mean sleep latency of 2.1 minutes and five sleep-onset rapid eye movement (REM) periods (including a nocturnal sleep-onset REM period), meeting the criteria for narcolepsy type 1.

COMMENT

This case illustrates some of the characteristic symptoms of narcolepsy type 1: severe daytime sleepiness, cataplexy (episodes of weakness triggered by an emotion, in this case, laughter), vivid dreams, and sleep paralysis. A detailed sleep history further revealed that the patient was getting irregular amounts of sleep, which contributed to some of the symptoms (specifically, daytime sleepiness and possibly sleep paralysis). However, since cataplexy is suggestive of narcolepsy type 1, further correction of sleep timings, reassessment of symptom severity, and evaluation with polysomnography with MSLT was important.

Insufficient sleep and delayed circadian rhythm disorder can result in decreased mean sleep latency and sleep-onset REM periods on the MSLT. Insufficient sleep prior to testing increases the risk of false-positive results and an incorrect diagnosis of narcolepsy. The correction of the patient's sleep schedule to allow for sufficient nocturnal sleep prior to formalized sleep testing with the MSLT was critical for accurate results.

asleep when one should be awake. People with fatigue may describe resting in bed during the day, but not falling asleep. The Epworth Sleepiness Scale[2] and the Epworth Sleepiness Scale for Children and Adolescents[3] can be quickly administered and are both commonly used in sleep clinics to identify sleepiness and assess its severity. Additionally, the Pediatric Hypersomnolence Survey is a free pediatric hypersomnolence screening survey for children 8 to 18 years old with 81% sensitivity and specificity for narcolepsy and idiopathic hypersomnia.[4] This survey can help clinicians order appropriate diagnostic testing or guide a referral to a sleep clinic. People with narcolepsy often report severe daytime sleepiness (typically associated with an Epworth Sleepiness Scale score of greater than 15 out of 24) with a proclivity to fall asleep in passive situations (eg, reading, attending a meeting or lecture, as a passenger in a car) and will occasionally have sudden sleep attacks or unpredictable, irrepressible urges to sleep. People with idiopathic hypersomnia often describe persistent low energy, feeling tired, and more moderate excessive daytime sleepiness (Epworth Sleepiness Scale score of 10 to 15 out of 24).[5]

Common causes of excessive daytime sleepiness are insufficient amounts of habitual sleep, other sleep disorders (eg, obstructive sleep apnea, insomnia, circadian rhythm sleep-wake disorders), and the adverse effects of medications. Sleep diaries[6] can identify whether adults are obtaining less than the recommended 7 hours of sleep per night for optimal daytime function[7] (pediatric sleep duration recommendations vary by age[8]) and if sleep timing is regular across weekdays and weekends (CASE 3-1). Actigraphy, a wristwatch device that estimates sleep and wake times based on movement patterns, is a helpful tool for collecting accurate data on habitual sleep patterns; clinical availability and insurance coverage for this modality vary. Inquiring about snoring, gasping, choking, and pauses in breathing during sleep, in addition to using screening tools such as the STOP-BANG Questionnaire, can help gauge clinical suspicion for obstructive sleep apnea and guide diagnostic testing.[9] The use of sedating medications and substances can also contribute to excessive daytime sleepiness. To prevent misdiagnoses and promote good stewardship of resources, practitioners should address these common causes of daytime sleepiness and reassess daytime sleepiness severity before embarking on testing for rarer central disorders of hypersomnolence.

Generally, unless the neurologic examination is abnormal, brain imaging is not conducted in the evaluation of narcolepsy or idiopathic hypersomnia. Imaging is indicated for the evaluation of sleepiness in the presence of focal neurologic dysfunction or encephalopathy, as lesions involving the brainstem, pineal gland, hypothalamus, or basal forebrain can cause sleepiness. Blood testing for thyroid function, erythrocyte sedimentation rate, and chemistries may be obtained when clinically relevant. Human leukocyte antigen (HLA) typing can be considered in the appropriate context as part of the evaluation for narcolepsy type 1; this will be discussed further in the narcolepsy section.

SLEEP STUDIES FOR EVALUATION OF HYPERSOMNOLENCE

In addition to the sleep history and clinical tools described above, central disorders of hypersomnolence are traditionally evaluated by overnight polysomnography followed by the multiple sleep latency test (MSLT). The exception is Kleine-Levin syndrome, which is a clinical diagnosis. The overnight polysomnogram helps to exclude other factors that contribute to daytime

KEY POINTS

- In the *International Classification of Sleep Disorders, Third Edition, Text Revision*, central disorders of hypersomnolence include narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia associated with a psychiatric disorder, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, and insufficient sleep syndrome.
- The Epworth Sleepiness Scale can be quickly administered and is commonly used to identify sleepiness and assess the severity of daytime sleepiness.
- Disorders of hypersomnolence are typically evaluated by overnight polysomnography followed by the multiple sleep latency test.

sleepiness such as sleep apnea or acute sleep deprivation (a minimum of 6 hours of sleep is required on overnight polysomnography to proceed with the MSLT) and to record rapid eye movement (REM) sleep latency, as this may support the diagnosis of narcolepsy. The MSLT consists of five 20-minute nap opportunities

TABLE 3-1 **Clinical Characteristics and Diagnostic Evaluation of Central Disorders of Hypersomnolence**

	Narcolepsy type 1	Narcolepsy type 2	Idiopathic hypersomnia	Kleine-Levin syndrome
Clinical presentation				
Onset	Adolescence (peak at 15 years old), sometimes childhood, another peak at 35 years old	Adolescence, sometimes childhood	Adolescence, twenties	Adolescence
Sex	Male = female	Male = female	Male = female	Male > female
Symptom pattern	Chronic	Chronic	Chronic	Episodic
Excessive daytime sleepiness	Always	Always	Always	Always, during an episode
Cataplexy	Often	Never	Never	Never
Sleep-related hallucinations	Often	Occasional	Occasional	Absent
Sleep paralysis	Often	Occasional	Occasional	Absent
Disrupted nighttime sleep	Often	Occasional	Rare	Absent
Prolonged sleep duration	Rare	Occasional	Often	Present during an episode
Sleep inertia	Rare	Occasional	Often	May be present during an episode
Daytime naps	Often, brief, refreshing	Variable	Often, long, unrefreshing	Variable, during an episode
Diagnostic evaluation				
Polysomnography and multiple sleep latency test	Sleep latency ≤8 min; two or more sleep-onset REM periods; or, a sleep-onset REM period within 15 min of sleep onset on nocturnal polysomnogram	Sleep latency ≤8 min; two or more sleep-onset REM periods	Sleep latency ≤8 min; no or one sleep-onset REM period Alternative: 11 sleep hours in a 24-hour polysomnogram, or average 11 sleep hours/night over 1 week of actigraphy	Not necessary for diagnosis
Orexin (hypocretin) in CSF	Low	Normal, sometimes intermediate	Normal	Normal

CSF = cerebrospinal fluid; REM = rapid eye movement.

every 2 hours throughout the day and measures sleep latency and sleep-onset REM periods. A mean sleep-onset latency of less than or equal to 8 minutes indicates hypersomnolence. More specific diagnostic criteria for narcolepsy and idiopathic hypersomnia are detailed below.

Strict protocols need to be reviewed for accurate polysomnography with MSLT.[10] Insufficient sleep, circadian rhythm disruption (including shift work), obstructive sleep apnea, and the use of marijuana, caffeine, and REM-suppressing medications (eg, clonidine, guanfacine, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic agents, antipsychotic medications) can alter polysomnogram and MSLT results, resulting in false positives or false negatives for narcolepsy or other hypersomnolence disorders.[11-14] To evaluate for sleep duration of less than 7 hours nightly in adults preceding the study, sleep diaries and actigraphy results, when available, should be collected over the 2 weeks prior to the sleep study.[10] Optimally, REM-suppressing medications and stimulants should be tapered and discontinued at least 2 weeks before the study; longer weaning periods are likely needed for medications with longer half-lives, such as fluoxetine.[10] In practice, patients or clinicians may be reluctant to discontinue medications due to the potential consequences of doing so, such as the worsening of underlying mood disorders. In these cases, testing is deferred to when the patient's mood is more stable and medications can be safely withheld, or the physician must interpret the results in the context of known medication effects. Alternative testing options can also be considered (see the section on narcolepsy below). For a more detailed description of sleep testing, refer to the article "Clinical Evaluation of the Sleepy and Sleepless Patient," by Samuel A. Taylor Jr, MD, MS,[15] in this issue of *Continuum*.

KEY POINTS

- Optimally, medications that impact sleep propensity and sleep architecture should be tapered and discontinued at least 2 weeks prior to the multiple sleep latency test.
- Many patients with narcolepsy have symptoms of rapid eye movement (REM) sleep intruding into their waking state, including cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis.
- Cataplexy is a generalized or partial loss of muscle tone, typically triggered by strong positive emotions, including laughter or anticipation.

PRIMARY CHRONIC CENTRAL NERVOUS SYSTEM DISORDERS OF HYPERSOMNOLENCE

Central disorders of hypersomnolence are characterized by excessive daytime sleepiness that impacts daily functions. Narcolepsy, idiopathic hypersomnia, and hypersomnia disorders associated with other medical or neurologic diseases are defined by chronic symptoms of sleepiness, while Kleine-Levin syndrome is characterized by episodic hypersomnolence.

Narcolepsy

Narcolepsy is a rare chronic neurologic disorder. People with narcolepsy typically present with severe or overwhelming urges to sleep during desired waking periods and, less commonly, sleep attacks. Many patients also experience symptoms of REM sleep intruding into waking periods, including cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis (TABLE 3-1).

Narcolepsy type 1 can be distinguished from narcolepsy type 2 by the presence of cataplexy or low orexin (hypocretin) levels in CSF (less than or equal to 110 pg/mL) in narcolepsy type 1 (TABLE 3-2).[1] Cataplexy is the generalized or partial loss of muscle tone, typically triggered by strong positive emotions, including laughter or anticipation. While anger is a less common trigger, other emotions that can trigger cataplexy include surprise, embarrassment, or fear; these triggers can change or become less frequent with age.[16] Cataplexy can also occur during intercourse or be related to orgasm, which can impact personal relationships.[17] Cataplexy may represent the intrusion of REM sleep physiology

(muscle atonia) into wakefulness.[18] Muscle involvement can be generalized, with slumping or slouching to the floor, or more commonly partial, with face, neck, or limb involvement resulting in droopy eyelids, slurred speech, or dropped head[19] (FIGURE 3-1[20]). The muscle weakness in cataplexy is bilateral, although it may be asymmetric,[18] and lasts seconds to minutes with complete subsequent recovery; no loss of consciousness is associated with these episodes. In children, cataplexy may be more complex, with positive motor activity or dyskinesias.[21] Status cataplecticus is rare, defined by prolonged cataplexy lasting hours and mainly occurring following the abrupt withdrawal of cataplexy-suppressing medications or insufficient sleep. Prolonged cataplexy can be a presenting symptom of narcolepsy in children. Typically, daytime sleepiness precedes or co-occurs with the first episode of cataplexy, although cataplexy can occur years or even decades after the onset of daytime sleepiness. Of note, delayed cataplexy is more common among African American people with narcolepsy type 1.[22] Cataplexy is commonly misdiagnosed as syncope, seizures, or psychogenic events[23] and video recordings of events can be helpful for diagnosis.

People with either narcolepsy type 1 or narcolepsy type 2 may describe episodic sleep paralysis and sleep-related hallucinations, with these symptoms being more common in narcolepsy type 1 than narcolepsy type 2.[24,25] Sleep paralysis is characterized by the inability to move one's arms or legs or the feeling that something heavy is pushing down on one's body, and typically occurs upon waking from sleep. These events typically last a few minutes; affected patients are awake during these episodes and have full recall after the event. Sleep paralysis may occur with sleep-related hallucinations, which can be unnerving. Sleep-related hallucinations refer to seeing or hearing things that are not there while falling asleep (hypnagogic) or waking up (hypnopompic); such hallucinations may include seeing a person, animal, or shape, and rarely involve

TABLE 3-2 **Features of Cataplexy**

Characteristic	Presentation of cataplexy
Appearance	Partial: drooping eyelids, slurred speech, dropped head
	General: slouching or slumping to the floor or a seated position
	Positive movements: dyskinetic movements or phasic muscle twitching (more prevalent in children)
Affected regions	Face, neck, limbs; bilateral
Tone, reflexes	Atonic, decreased or absent reflexes in affected areas
Duration	Seconds to minutes
Level of consciousness	Fully conscious; full event recall
Trigger	Strong emotions, usually positive (eg, laughter, anticipation, surprise)
Cause	Strongly associated with narcolepsy type 1
	Also seen in Niemann-Pick disease type C, Angelman syndrome, Norrie disease, Prader-Willi syndrome, hypothalamic lesions, paraneoplastic encephalitis (anti-Ma2 autoantibodies)

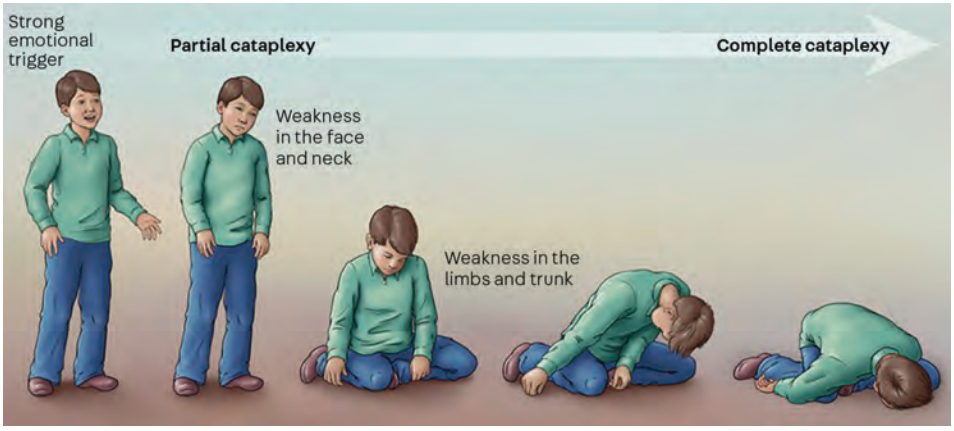

FIGURE 3-1

Cataplexy is transient weakness of the face, neck, or limbs (partial) or the whole body (generalized), triggered by emotion.

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KEY POINTS

- **The narcolepsy tetrad of sleepiness, cataplexy, sleep paralysis, and sleep-related hallucinations is present in only about 45% of people with narcolepsy type 1.**
- **People with narcolepsy have disrupted nocturnal sleep, with increased arousal index, sleep stage transitions, and time spent awake after sleep onset relative to healthy sleepers.**
- **Patients with narcolepsy are at increased risk of developing medical and psychiatric comorbidities, including obesity and hypertension; depression has been reported in more than one-third of patients with narcolepsy.**

auditory and tactile components.[24,25] Sleep paralysis and sleep-related hallucinations can occur in otherwise healthy people when provoked by sleep deprivation or circadian rhythm misalignment.[26] The narcolepsy tetrad of sleepiness, cataplexy, sleep paralysis, and sleep-related hallucinations is present in approximately 45% of people with narcolepsy type 1, but all four features are rarely present at the time of the initial clinical evaluation.[25]

Patients with narcolepsy often have other sleep symptoms that disturb sleep quality, a general term referred to as disrupted nighttime sleep.[27] Sleep instability is a central feature of narcolepsy type 1 and is closely associated with orexin (hypocretin) levels.[27,28] People with narcolepsy have increased arousal index, sleep stage transitions, and time spent awake after sleep onset relative to people without narcolepsy.[29,30] Narcolepsy type 1 is characterized by more arousals from sleep and lower overall sleep efficiency compared with either narcolepsy type 2 or idiopathic hypersomnia.[30] Vivid or lucid dreams (ie, dreams that a person is consciously aware of dreaming) are frequently reported by people with narcolepsy[31]; occasionally, dreams are so realistic that they produce false memories or dream-reality confusion.[32] Either clinical dream enactment behavior or REM sleep without atonia seen on polysomnogram can be present in 20% to 60% of people with narcolepsy.[33,34] Other comorbid sleep disorders include obstructive sleep apnea, periodic limb movement disorder, and restless legs syndrome.[35] People with narcolepsy have an increased risk of medical and psychiatric comorbidities including obesity, hypertension, endocrinopathies, headaches, chronic pain, and diabetes; depression has been reported in over 30% of patients with narcolepsy at time of diagnosis, with rates increasing to 50% over time.[36] To help guide the management of narcolepsy and evaluate treatment response, validated clinical scales are now available to assess narcolepsy symptom severity, daily function, and symptom burden.[37,38]

EPIDEMIOLOGY. The prevalence of narcolepsy type 1 is 1 in 2000, or 0.05%,[39] and affects males and females equally. The typical age of onset is bimodal with peaks at approximately 15 and 35 years old[40]; however, years of delay may occur between symptom onset and diagnosis.[41] The prevalence of narcolepsy type 2 is

complicated because MSLT is needed for diagnosis and there are no specific distinguishing features (such as cataplexy or specific orexin [hypocretin] levels in CSF). Based on a recent analysis of a US medical claims database of over 8 million patients[42] and data from the Wisconsin Sleep Cohort study,[15] the prevalence of narcolepsy type 2 is approximately 2 to 4 times greater than that of narcolepsy type 1.

PATHOPHYSIOLOGY. Narcolepsy type 1 is likely caused by immune-mediated selective loss of orexin (hypocretin)-producing neurons in the hypothalamus.[42] Orexin (hypocretin) is a peptide that promotes wakefulness and coordinates sleep-stage transition stability. Evidence supporting immune-mediated loss of these neurons includes association with specific HLA alleles (the strongest association being with HLA-DQB1*06:02)[43] and identification of activated T cells in patients with narcolepsy type 1.[44] Additionally, associations between narcolepsy type 1 and T-cell function have been identified in genome-wide association studies, including components of T-cell antigen presentation and recognition.[45] Seasonal variation of narcolepsy type 1 onset,[46] association with influenza A (H1N1) infection and some forms of the H1N1 vaccine,[47] as well as association of narcolepsy type 1 with other infections further support an immune-mediated etiology.[43] The pathophysiology of narcolepsy type 2 is not clear. About 20% of people initially diagnosed with narcolepsy type 2 eventually develop orexin (hypocretin) deficiency or cataplexy,[48] which suggests that narcolepsy type 2 can be an intermediate diagnosis, eventually leading to the diagnosis of narcolepsy type 1. For most people with narcolepsy type 2, orexin (hypocretin) levels are normal, although there may be partial loss of orexin (hypocretin) neurons and mildly lower than normal orexin (hypocretin) levels in CSF.[49]

DIAGNOSIS. Narcolepsy type 2 requires a clinical history of excessive daytime sleepiness for 3 months. Narcolepsy type 1 can present abruptly with symptoms developing over days to weeks. This presentation occurs more commonly in children. Accordingly, symptom duration is not specified in the latest diagnostic criteria for narcolepsy type 1. Narcolepsy type 1 requires a confirmatory polysomnogram or MSLT result and a history of cataplexy or orexin (hypocretin) levels less than or equal to 110 pg/mL in CSF, and the diagnosis of narcolepsy type 2 is confirmed with MSLT.[1] Narcolepsy type 2, by definition, implies the absence of cataplexy and normal orexin (hypocretin) levels in CSF, in addition to the confirmatory MSLT result. Specific criteria for narcolepsy type 2 include the absence of features seen in narcolepsy type 1 (either cataplexy or low CSF orexin [hypocretin]). Like narcolepsy type 1, narcolepsy type 2 requires a clinical history of excessive daytime sleepiness and a confirmatory MSLT. MSLT results consistent with both narcolepsy type 1 and narcolepsy type 2 include a mean sleep-onset latency of 8 minutes or less and two or more sleep-onset REM periods.[1] A nocturnal sleep-onset REM period (REM sleep within 15 minutes of sleep-onset on the baseline polysomnogram that precedes the MSLT) can be included in the tally of sleep-onset REM periods and is a highly specific biomarker for narcolepsy type 1 in adults and children.[50,51] A nocturnal sleep-onset REM period is now included in the *ICSD-3-TR* as an alternative diagnostic criterion to two sleep-onset REM periods on MSLT for narcolepsy type 1. Over 90% of people with narcolepsy type 1 have low orexin (hypocretin) in CSF.[52] If a patient with suspected narcolepsy type 2 has CSF testing that shows low orexin

(hypocretin), the diagnosis changes to narcolepsy type 1, even if cataplexy is not present. Newer research has highlighted several nocturnal sleep diagnostic biomarkers for diagnosing narcolepsy type 1 in children and adults based on features of disrupted nighttime sleep[53,54] and dysregulated REM sleep.[33,55] Furthermore, the application of artificial intelligence to polysomnography for narcolepsy type 1 has preliminarily demonstrated robust diagnostic sensitivity (91%) and specificity (96%),[56] and such advancements may make the MSLT unnecessary in the future.

HLA-DQB1*06:02 is the most common genetic marker for narcolepsy across all ethnic groups, and it is found in 85% to 95% of people with narcolepsy type 1.[57] HLA typing can be helpful in screening for narcolepsy type 1 and conveying likely autoimmune etiology to patients. In narcolepsy type 2, only 40% of people have HLA-DQB1*06:02,[58] so HLA testing in these patients is generally unhelpful. However, given that cataplexy can develop years after the onset of excessive daytime sleepiness,[52] the authors find HLA typing to be useful in the prognostication of symptom burden. Importantly, this genetic test alone is insufficient for the diagnosis of narcolepsy as HLA-DQB1*06:02 is found in 12% to 25% of the general population.

While the MSLT has high diagnostic validity and reliability for patients with narcolepsy type 1,[59] there is poor reliability for narcolepsy type 2[60] and idiopathic hypersomnia.[59,61] It is unclear if this poor reliability is due to the unstable disease state or problems in protocol adherence. Medications that are sedating or stimulating or that alter REM sleep timing can impact MSLT results for a narcolepsy diagnosis. Sleep-onset REM periods can be decreased by SSRIs, SNRIs, tricyclic antidepressants,[14,62] and antipsychotic medications if used at the time of testing, and sleep-onset REM periods can increase in the context of abrupt discontinuation or even tapering off of these agents prior to the MSLT.[63]

SECONDARY NARCOLEPSY. Excessive daytime sleepiness with cataplexy is quite specific for narcolepsy type 1; however, nonspecific damage to the orexin (hypocretin) neurons or their pathways by trauma, malignancy, inflammation, or infection can cause secondary narcolepsy with or without cataplexy in both adults and children.[64,65] Excessive daytime sleepiness with cataplexy has also been described in paraneoplastic or autoimmune encephalitis, particularly associated with anti-Ma2 autoantibodies.[66] People with cataplexy who have focal neurologic deficits or encephalopathy merit further evaluation with brain MRI to evaluate for secondary narcolepsy.

In addition to structural lesions of the hypothalamus, cataplexy can be seen in the pediatric genetic syndromes Niemann-Pick disease type C, Angelman syndrome, Norrie disease, Prader-Willi syndrome, myotonic dystrophy, and DNMT1-complex disorder.[67]

Idiopathic Hypersomnia

Idiopathic hypersomnia is clinically characterized by excessive daytime sleepiness, severe difficulty waking from sleep (sleep inertia), and daytime brain fog or cognitive cloudiness. Descriptions of excessive daytime sleepiness are variable, including severe urges to sleep during the day, generalized low energy or fatigue, or prolonged nocturnal sleep duration. In contrast to narcolepsy, where total sleep duration over the 24-hour day is normal (7.5 to 8 hours per day),[68] patients with idiopathic hypersomnia can have prolonged sleep duration

KEY POINTS

- Narcolepsy type 1 is likely caused by immune-mediated selective loss of orexin (hypocretin)-producing neurons in the hypothalamus.
- The multiple sleep latency test has high diagnostic validity and reliability in narcolepsy; however, the reliability is poor in narcolepsy type 2 and idiopathic hypersomnia.
- Cataplexy can be seen in the pediatric genetic syndromes Niemann-Pick disease type C, Angelman syndrome, Norrie disease, Prader-Willi syndrome, DNMT1-complex disorder, and myotonic dystrophy.
- Idiopathic hypersomnia is clinically characterized by excessive daytime sleepiness, severe difficulty waking from sleep (sleep inertia), and daytime brain fog or cognitive cloudiness.
- Patients with idiopathic hypersomnia can have prolonged sleep duration with more than 10 to 11 hours of nocturnal sleep in addition to long daytime naps.

with more than 10 to 11 hours of nocturnal sleep plus long daytime naps.[69,70] In contrast to narcolepsy, patients with idiopathic hypersomnia usually describe prolonged, unrefreshing daytime naps.[71] While prolonged sleep can be seen in patients with narcolepsy, this is predominantly seen in narcolepsy type 2 and is in the minority of patients with either narcolepsy type 1 or narcolepsy type 2.[69] In the *International Classification of Sleep Disorders, Second Edition*,[72] idiopathic hypersomnia was divided into idiopathic hypersomnia with or without prolonged sleep duration, but in the most recent *ICSD-3-TR* no distinction between the two is made. However, evolving evidence shows that idiopathic hypersomnia with prolonged sleep duration and idiopathic hypersomnia without prolonged sleep duration differ in terms of sleep architecture, comorbidities, and treatment response.[70,73]

Severe sleep inertia, or difficulty rising from sleep in the morning, is another symptom seen primarily in idiopathic hypersomnia.[74] Sleep inertia is brief in people with healthy sleep, but in patients with idiopathic hypersomnia this period is both prolonged and pronounced. Sleep inertia in idiopathic hypersomnia is also referred to as sleep drunkenness, due to cognitive dysfunction and clumsiness of movement. Difficulty waking up in the morning can be so pronounced that patients require the assistance of another person to wake them.[5]

Clinical scales have been validated for idiopathic hypersomnia and can be useful in assessing symptom severity, symptom burden, and treatment response.[75]

TABLE 3-3 ***ICSD-3-TR* Diagnostic Criteria for Idiopathic Hypersomnia[a]**

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria A through F must be met for an idiopathic hypersomnia diagnosis:**

- **A The patient has daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep occurring or at least three months.**
- **B Cataplexy is absent.**
- **C Polysomnography and MLST findings are not consistent with narcolepsy type 1 or 2.**
- **D The presence of at least one of the following:**
  - 1 The MSLT, performed in accordance with current recommended protocols, shows a mean sleep latency of less than or equal to 8 minutes.
  - 2 Total 24-hour sleep time of 660 minutes or longer (typically 12 to 14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), *or* by wrist actigraphy in association with a sleep diary (averaged over at least 7 days with unrestricted sleep).
- **E Insufficient sleep is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy).**
- **F The symptoms and signs are not better explained by a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication/substance use withdrawal.**

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EPIDEMIOLOGY. Idiopathic hypersomnia is thought to be a rare disease, although the estimated prevalence is limited by heterogeneous symptoms and diagnostic limitations of the MSLT.[60,61] It is estimated to be about one-tenth to one-half as common as narcolepsy, with 20 to 50 cases per million.[71,76] Symptoms often begin in the patient's second decade[77]; although typically no preceding trauma or illness is identified, a subset of people with idiopathic hypersomnia report symptom onset after a preceding illness or minor head trauma.[71,78] Based on a disease registry survey, idiopathic hypersomnia may have a higher prevalence in non-Hispanic White women, but the demographics may be biased based on survey respondents.[77]

PATHOPHYSIOLOGY. The physiology underlying the symptoms of idiopathic hypersomnia is not well understood. Orexin (hypocretin) levels are normal in patients with idiopathic hypersomnia. Several hypotheses exist regarding possible mechanisms that may underlie idiopathic hypersomnia, including enhanced γ-aminobutyric acid (GABA) responsiveness, autonomic dysfunction, and circadian rhythm disruption. One hypothesis involves abnormal γ-aminobutyric acid–mediated (GABA-ergic) responsivity, with increased $GABA_A$ receptor potentiation relative to controls, but these results have not been consistent across studies.[79] Medications that modulate $GABA_A$ receptors can decrease sleepiness in some people with idiopathic hypersomnia,[80,81] which plausibly supports $GABA_A$ receptor dysfunction as causative of symptoms in a subset of diagnosed patients. A second hypothesis is that dysautonomia may underlie idiopathic hypersomnia physiology; patients with idiopathic hypersomnia have increased autonomic symptoms relative to controls[5,82] and an increased parasympathetic-to-sympathetic activity ratio in a study of heart rate variability.[83] Alternatively, idiopathic hypersomnia may represent a circadian rhythm disorder, with data supporting a "long biologic night" and a prolonged circadian period in skin fibroblasts collected from patients with idiopathic hypersomnia[84] and a decreased amplitude of expression of the circadian genes *BMAL1*, *PER1*, and *PER2*.[85] Part of the challenge in identifying the etiology of idiopathic hypersomnia may be the heterogeneity in the patient population, which may reflect diverse pathophysiology.

Debate is ongoing regarding the relationship between narcolepsy type 2 and idiopathic hypersomnia because a subset of these patients may share common physiologic features.[86] Patients with either diagnosis may present with similar clinical phenotypes, and current diagnostic differentiation is based on the presence of sleep-onset REM periods during the MSLT.

DIAGNOSIS. In recognition of the heterogeneity of the idiopathic hypersomnia phenotype, the *ICSD-3-TR* offers multiple ways to meet diagnostic criteria, as shown in TABLE 3-3.[1]

For patients with idiopathic hypersomnia, the sensitivity of the MSLT is low and the test-retest reliability is poor.[60,61] Long sleep time measured by extended polysomnography may have superior sensitivity in idiopathic hypersomnia[87]; however, while these 24- to 36-hour protocols provide improved diagnostic accuracy and reliability, they are rarely feasible and currently not reimbursed, and thus are not commonly available for diagnostic purposes. Actigraphy uses motion to estimate sleep-wake patterns and has been studied in central disorders of hypersomnolence[88]; while it has the advantage of estimating sleep-wake

KEY POINTS

- The physiology underlying the symptoms of idiopathic hypersomnia is not well understood and could reflect modified γ-aminobutyric acid (GABA) responsiveness, dysautonomia, or circadian rhythm dysfunction.
- Patients diagnosed with either narcolepsy type 2 or idiopathic hypersomnia may present with similar clinical phenotypes, and current diagnostic differentiation is based on the presence of sleep-onset REM periods during the multiple sleep latency test.

patterns in the home setting, it is not widely available due to cost and limited reimbursement. Of note, this diagnostic pathway is based only on clinical actigraphs, not direct-to-consumer sleep technologies.[89] The lack of feasible and valid diagnostic testing for idiopathic hypersomnia is a barrier to the diagnosis and treatment of these patients (CASE 3-2).

Management of Narcolepsy and Idiopathic Hypersomnia

Existing therapies for chronic central disorders of hypersomnolence target symptom control since no disease-modifying therapies exist for these diagnoses. Conditions such as narcolepsy and idiopathic hypersomnia are lifelong. The therapeutic goal is to improve excessive daytime sleepiness and other burdensome symptoms to optimize academic, social, family, and workplace function. Pharmacologic and behavioral approaches can mitigate daytime sleepiness severity. Medications should be selected considering possible short-term and long-term adverse effects, cost, and risk-benefit to the patient. Education about these disorders and lifestyle adjustments, such as maintaining a regular sleep-wake schedule with adequate sleep opportunity to avoid sleep deprivation, provision of school and work accommodations, and scheduling daytime naps, are important for patients with chronic central disorders of hypersomnolence. For patients with narcolepsy, scheduled daytime naps of 15 to

CASE 3-2

A 26-year-old woman presented to the sleep clinic with excessive daytime sleepiness. She had difficulty focusing on work tasks and would often take a 2- to 3-hour nap after work. Despite the evening nap, she could easily fall asleep again at bedtime, and typically slept 9 to 10 hours each night. She would set six alarms at 10-minute intervals for the morning, and after getting out of bed she felt "slow" and "groggy" until she finished breakfast. This sleep pattern had been present since college, though she had been able to adapt by scheduling her classes around her sleep schedule. On nonwork days, she would often sleep 14 hours, and take a 2- to 3-hour nap in the afternoon. While she felt "tired" all day, she did not fall asleep during work. She was diagnosed with depression when she was in high school and was taking fluoxetine. Her Epworth Sleepiness Scale score was 13 out of 24 (indicating moderate daytime sleepiness).

A polysomnogram with multiple sleep latency test (MSLT) was ordered; however, as the results of this test can be impacted by rapid eye movement (REM)-modulating medications (including fluoxetine), her physician discussed tapering the fluoxetine prior to the sleep study. The patient was comfortable coming off fluoxetine for 2 weeks preceding the sleep study. In preparation for the sleep study, she kept a 2-week sleep diary, which confirmed the sleep pattern that she described. The polysomnogram with MSLT showed a mean sleep latency of 7.2 minutes and no sleep-onset REM periods (REM sleep latency for the overnight polysomnogram was 65 minutes), meeting the criteria for idiopathic hypersomnia.

30 minutes can partially ameliorate drowsiness and improve alertness; naps are typically less helpful for sleepiness related to idiopathic hypersomnia. The American Academy of Sleep Medicine guidelines for the treatment of central disorders of hypersomnolence include recommendations for adult and pediatric narcolepsy and idiopathic hypersomnia and classify strong and conditional recommendations based on available evidence.[90] Additionally, the joint European guidelines incorporate evidence with expert opinion to present first-line and second-line recommendations.[91] Choices about medications should consider the most bothersome symptoms, medical comorbidities, and patient preferences. Pharmacologic treatments available for excessive daytime sleepiness in narcolepsy and idiopathic hypersomnia and for cataplexy in narcolepsy type 1 are summarized in **TABLE 3-4**,[90] **TABLE 3-5**,[90] and **TABLE 3-6**, respectively.

Modafinil, pitolisant, solriamfetol, and oxybates (sodium oxybate and lower-sodium oxybate) are reasonable to consider as first-line therapy for adult patients with excessive daytime sleepiness. Per the European guidelines, monotherapy with pitolisant (for milder symptoms) or oxybates (for more severe symptoms) is reasonable to consider as first-line therapy for patients with excessive daytime sleepiness and cataplexy.[91] REM-suppressing antidepressants, in particular venlafaxine and fluoxetine, are frequently used off-label to reduce cataplexy.[92] Combination therapy with a wake-promoting agent and an

COMMENT

Daytime sleepiness and morning sleep inertia are seen in idiopathic hypersomnia. *Sleep inertia* refers to difficulty waking up in the morning; sometimes people with idiopathic hypersomnia require the assistance of another person or multiple alarms to wake up in the morning and can experience clumsiness or say insensible things soon after waking up ("sleep drunkenness"). Additionally, cognitive clouding or "brain fog" are frequently described during the day. In contrast with narcolepsy, daytime naps tend to be long and nonrefreshing. Epworth Sleepiness Scale scores are often moderate in severity.

It is important for patients to get a sufficient amount of sleep prior to the sleep study (8 hours or more) and be allowed to sleep their habitual amount (in this case, a minimum of 9 hours) on the polysomnogram prior to the MSLT. Home sleep duration can be tracked using sleep diaries, validated sleep wearables such as actigraphy, or both. Insufficient sleep prior to the sleep studies or on the polysomnogram itself could result in REM rebound during the MSLT and the potential for a false-positive diagnosis of narcolepsy. Common medications, including selective serotonin reuptake inhibitors (SSRIs), can modulate REM sleep and, if possible, should be tapered before the polysomnogram and MSLT. Fluoxetine and other SSRIs may result in REM sleep suppression on the MSLT, making it difficult to distinguish idiopathic hypersomnia from narcolepsy (especially with no clinical history of cataplexy).

TABLE 3-4 **Treatment of Excessive Daytime Sleepiness in Narcolepsy**

Strength of recommendation[a]	Therapeutic dose (adult)	Demonstrated clinical improvement measures and comments	Adverse effects	Monitoring
Strong				
Modafinil	200 mg to 400 mg, once daily or divided two times a day	Excessive daytime sleepiness, disease severity, quality of life	Common: headache, nausea, insomnia Rare: severe rash (Stevens-Johnson syndrome)	Monitor blood pressure CYP3A4/CYP3A5 enzyme induction: impairs effectiveness of steroidal contraceptives Exposure during pregnancy increases risk of congenital malformations
Pitolisant	17.8 mg or 35.6 mg daily	Excessive daytime sleepiness, cataplexy, disease severity	Common: headache, insomnia, anxiety, GI upset Rare, serious: QT interval prolongation	Monitor QT interval
Sodium oxybate, oxybate salts (lower-sodium oxybate)	6 g to 9 g per night, divided (starting dose 4.5 g/night) Taken at bedtime and 2.5 to 4 hours later	Excessive daytime sleepiness, cataplexy, disease severity Approved for children	Common: morning sedation, nausea, weight loss, dizziness, enuresis, sleepwalking, tremor, constipation, worsening of sleep-disordered breathing Rare, serious: confusion, severe sedation, coma, depression, suicidal ideation, psychosis	Not to be used with alcohol, sedatives, or hypnotics Central pharmacy with enrollment in Risk Evaluation and Mitigation Strategies program Potential for diversion and abuse; overdose can result in seizures, coma, or death
Solriamfetol	75 mg or 150 mg daily	Excessive daytime sleepiness, disease severity, quality of life	Common: headache, GI upset, anxiety, constipation, dry mouth, palpitations	Monitor heart rate and blood pressure

CONTINUED ON PAGE 1059

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Strength of recommendation[a]	Therapeutic dose (adult)	Demonstrated clinical improvement measures and comments	Adverse effects	Monitoring
Conditional				
Armodafinil	150 mg to 250 mg daily	Excessive daytime sleepiness, disease severity	Common: headache, nausea, insomnia Rare: severe rash (Stevens-Johnson syndrome)	Monitor blood pressure CYP3A4/CYP3A5 enzyme induction: impairs effectiveness of steroidal contraceptives Exposure during pregnancy increases risk of congenital malformations
Dextroamphetamine	Immediate release: 5 mg to 60 mg/day in one to three divided doses (4- to 6-hour intervals) Extended release: 10 mg to 60 mg in one to two divided doses (8-hour interval)	Excessive daytime sleepiness, cataplexy Approved for children	Common: irritability, anxiety, anorexia, weight loss, sleep disturbance, jitteriness, emotional lability Rare, serious: psychosis, mania, seizure, priapism, cardiovascular effects "Wearing off" or rebound sleepiness in the afternoon	Due to insomnia, final dose of the day no later than 4 to 6 hours before bedtime Monitor weight, blood pressure; caution if family or personal history of cardiac arrhythmias Addictive potential at higher doses, potential for tolerance or abuse
Methylphenidate	Immediate release: 10 mg to 60 mg/day in two to three divided doses Extended release: 10 mg to 60 mg/ day Other intermediate and long-acting formulations available	Disease severity Approved for children	Common: irritability, anxiety, anorexia, weight loss, sleep disturbance, jitteriness, emotional lability Rare, serious: psychosis, mania, seizure, priapism, cardiovascular effects "Wearing off" or rebound sleepiness in the afternoon	Due to insomnia, final dose of the day no later than 4-6 hours before bedtime Monitor weight, blood pressure; caution if family or personal history of cardiac arrhythmias Addictive potential at higher doses, potential for tolerance or abuse

CONTINUED ON PAGE 1060

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Strength of recommendation[a]	Therapeutic dose (adult)	Demonstrated clinical improvement measures and comments	Adverse effects	Monitoring
No data to support strength of recommendation				
Lisdexamfetamine	30 mg to 70 mg/day	Approved for children	Common: irritability, anxiety, anorexia, weight loss, sleep disturbance, jitteriness, emotional lability Rare, serious: psychosis, mania, seizure, priapism, cardiovascular effects "Wearing off" or rebound sleepiness in the afternoon	Due to insomnia, final dose of the day no later than 4-6 hours before bedtime Monitor weight, blood pressure; caution if family or personal history of cardiac arrhythmias Addictive potential at higher doses, potential for tolerance or abuse
Amphetamine/ dextroamphetamine	Immediate release: 10 mg to 60 mg/day, in two to three divided doses (4- to 6-hour intervals) Long-acting formulations available	Approved for children	Common: irritability, anxiety, anorexia, weight loss, sleep disturbance, jitteriness, emotional lability Rare, serious: psychosis, mania, seizure, priapism, cardiovascular effects "Wearing off" or rebound sleepiness in the afternoon	Due to insomnia, final dose of the day no later than 4 to 6 hours before bedtime Monitor weight, blood pressure; caution if family or personal history of cardiac arrhythmias Addictive potential at higher doses, potential for tolerance or abuse

CYP = cytochrome P450; GI = gastrointestinal.

[a] The strength of recommendation from the American Academy of Sleep Medicine Clinical Practice Guidelines[90] is based on the clinical significance of the critical outcomes and the overall assessment of quality of evidence, balance of benefit and harm, patient values and preferences, and resource use. Limited data exist on the safety of any of these medications in pregnancy; modafinil increases the risk of serious congenital malformations.

antidepressant can be considered as an alternative to oxybates to treat sleepiness and cataplexy. Oxybates are the most efficacious for improving sleep quality in patients with disrupted nocturnal sleep.

Modafinil improves sleepiness, disease severity, and quality of life in patients with narcolepsy, improves sleepiness and disease severity in idiopathic hypersomnia, and is generally well tolerated.[90] Modafinil and its active R-enantiomer, armodafinil, promote wakefulness primarily by blocking dopamine reuptake through binding to the dopamine transporter.[93] Armodafinil similarly improves daytime sleepiness and disease severity in narcolepsy.[94] For people of childbearing potential, counseling regarding decreased efficacy of steroidal contraceptives with modafinil and armodafinil is critical. Modafinil is

not recommended for use during pregnancy due to the increased incidence of congenital malformations with exposure.[95] Modafinil is effective in the treatment of idiopathic hypersomnia with normal sleep time, but is less effective in those with long sleep times.[96] In another recent multicenter, randomized, placebo-controlled, parallel group study of patients with idiopathic hypersomnia without long sleep duration, objective measures of excessive daytime sleepiness improved with modafinil treatment without clinically significant adverse effects.[97]

Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor and, like modafinil, significantly improves daytime sleepiness, disease severity, and quality of life in patients with narcolepsy type 1 and narcolepsy type 2.[98]

Stimulants including amphetamines (eg, dextroamphetamine, mixed amphetamine salts) and amphetaminelike drugs (eg, methylphenidate) promote wakefulness and improve excessive daytime sleepiness; they have been a mainstay of narcolepsy treatment for many years. Traditional stimulants (ie, amphetamine derivatives and methylphenidate) also improve symptoms of idiopathic hypersomnia.[99] These medications are often used for the treatment of daytime sleepiness in pediatric narcolepsy because they are US Food and Drug Administration (FDA) approved for this indication. A paucity of clinical trial data and longitudinal data exist in the pediatric narcolepsy population to assess the risk-benefit of traditional stimulants; clinical experience supports their effectiveness, but monitoring is required due to short-term adverse effects of weight loss, elevated blood pressure, headache, increased anxiety, and insomnia.

For patients with problematic sleepiness and cataplexy, pitolisant, a histamine H_3 receptor inverse agonist, can improve sleepiness[100] and reduce cataplexy by 75%.[101] Pitolisant can also improve sleepiness in people with idiopathic hypersomnia.[102]

Oxybates (sodium oxybate and lower-sodium oxybate) reduce sleepiness, disrupted nocturnal sleep, and cataplexy in patients with narcolepsy. Sodium oxybate is the sodium salt of γ-hydroxybutyrate. The lower-sodium oxybate is a mix of calcium, magnesium, potassium, and sodium oxybates that was FDA approved for narcolepsy and idiopathic hypersomnia in 2021. Both formulations are effective for reducing daytime sleepiness, possibly through sleep consolidation and increased deep sleep.[103] Lower-sodium oxybate was studied in a multicenter study of 154 adults with idiopathic hypersomnia and showed improvement of excessive daytime sleepiness on the Epworth Sleepiness Scale from the end of the stable-dose period to the end of the double-blind randomized withdrawal period.[104] In the same trial, lower-sodium oxybate was associated with benefits to overall idiopathic hypersomnia symptoms and patient impression of symptom severity.[104] Lower-sodium oxybate should be preferentially used if concern exists about the high sodium content of standard sodium oxybate (at the maximal dose of 9 mg/day, standard sodium oxybate contains about 1640 mg/day sodium compared to only 131 mg/day sodium in lower-sodium oxybate), such as for patients with elevated blood pressure. Both sodium oxybate and lower-sodium oxybate are FDA approved for the treatment of pediatric narcolepsy. Oxybates are administered by an FDA Risk Evaluation and Mitigation Strategy program through a central pharmacy.

Clarithromycin, which is a negative allosteric modulator of $GABA_A$ receptors, has been shown to reduce daytime sleepiness in clinical trials of idiopathic hypersomnia.[80] For patients with severe sleep inertia, the use of stimulants at bedtime may reduce sleep inertia in the morning. An improved understanding of

KEY POINTS

- **Scheduled daytime naps of 15 to 30 minutes can partially ameliorate drowsiness and improve alertness for patients with narcolepsy; naps are typically less helpful for sleepiness related to idiopathic hypersomnia.**
- **Oxybates (sodium oxybate and lower-sodium oxybate) reduce sleepiness, disrupted nocturnal sleep, and cataplexy in patients with narcolepsy.**

the physiology that underlies sleep-wake disturbances in these patients may direct the development of targeted therapies.

HYPERSOMNIA DISORDERS ASSOCIATED WITH OTHER MEDICAL AND NEUROLOGIC DISEASES

Profound changes in sleep patterns can emerge with systemic illness and neurologic diseases. Symptoms of prolonged nocturnal sleep or increased daytime sleepiness can increase morbidity associated with these disorders and reflect potential opportunities for therapeutic intervention.

Hypersomnolence Related to α-Synucleinopathies

Fatigue and daytime sleepiness, as well as disrupted nocturnal sleep, are present in Parkinson disease and dementia with Lewy bodies. Daytime sleepiness

TABLE 3-5 **Treatment of Excessive Daytime Sleepiness in Idiopathic Hypersomnia**

Strength of recommendation[a]	Therapeutic dose (adult)	Demonstrated clinical improvement measures and comments	Adverse effects	Monitoring
Strong				
Modafinil	200 mg to 400 mg daily or divided into two times a day	Excessive daytime sleepiness, disease severity	Common: headache, nausea, insomnia Rare: severe rash (Stevens-Johnson syndrome)	Monitor blood pressure CYP3A4/CYP3A5 enzyme induction: impairs effectiveness of steroidal contraceptives Exposure during pregnancy increases risk of congenital malformations
Conditional				
Clarithromycin	500 mg 2 times a day	Excessive daytime sleepiness, disease severity, quality of life	Common: dysgeusia, dysosmia, GI upset, insomnia, QT interval prolongation	Monitor QT interval
Methylphenidate	Immediate release: 10 mg to 60 mg/day in two to three divided doses Extended release: 10 mg to 60 mg/day Other intermediate and long-acting formulations available	Disease severity Approved for children	Common: irritability, anxiety, anorexia, weight loss, sleep disturbance, jitteriness, emotional lability Rare, serious: psychosis, mania, seizure, priapism, cardiovascular effects "Wearing off" or rebound sleepiness in the afternoon	Monitor blood pressure; caution if family or personal history of cardiac arrhythmias Addictive potential at higher doses, potential for tolerance or abuse

CONTINUED ON PAGE 1063

can occur in addition to prolonged nocturnal sleep or, more commonly, fragmented nocturnal sleep. Treatments include many of the same medications used to treat sleepiness in narcolepsy. For patients with sleepiness associated with Parkinson disease, modafinil[104] and armodafinil[105] are well tolerated and may improve daytime sleepiness. Sodium oxybate also improves daytime sleepiness in Parkinson disease,[106] although caution must be used given the adverse effects. Bright light therapy may also improve daytime sleepiness in this population.[107]

Posttraumatic Brain Injury Hypersomnolence

Sleep-wake disturbances are common following traumatic brain injury. While insomnia is the most common concern, excessive daytime sleepiness or prolonged sleep duration is also seen in 40% of patients following brain injury.[108]

CONTINUED FROM PAGE 1062

Strength of recommendation[a]	Therapeutic dose (adult)	Demonstrated clinical improvement measures and comments	Adverse effects	Monitoring
Pitolisant	17.8 mg or 35.6 mg daily	Excessive daytime sleepiness	Common: headache, insomnia, anxiety, GI upset Rare, serious: QT interval prolongation	Monitor QT interval
Sodium oxybate, oxybate salts (lower-sodium oxybate)	6 g to 9 g per night divided (starting dose 4.5 g/night). Taken at bedtime and 3 to 4 hours later	Excessive daytime sleepiness Oxybate salts: specific FDA indication for idiopathic hypersomnia	Common: morning sedation, nausea, weight loss, dizziness, enuresis, sleepwalking, tremor, constipation, worsening of sleep-disordered breathing Rare, serious: confusion, severe sedation, coma, depression, suicidal ideation, psychosis	Not to be used with alcohol, sedatives, or hypnotics Central pharmacy with enrollment in Risk Evaluation and Mitigation Strategies program Potential for diversion and abuse; overdose can result in seizures, coma, or death

CYP = cytochrome P450; FDA = US Food and Drug Administration; GI = gastrointestinal.

[a] The strength of recommendation from the American Academy of Sleep Medicine Clinical Practice Guidelines[90] is based on the clinical significance of the critical outcomes and the overall assessment of quality of evidence, balance of benefit and harm, patient values and preferences, and resource use. Limited data exist on the safety of any of these medications in pregnancy; modafinil increases the risk of serious congenital malformations.

For daytime sleepiness in posttraumatic hypersomnolence, modafinil[109] and armodafinil[110] improve subjective and objective measures of daytime sleepiness.

COVID-19

In the wake of the COVID-19 pandemic, patients with postacute COVID-19 syndrome ("long haulers") most commonly describe tiredness or fatigue, postexertional malaise, and respiratory or neurologic symptoms.[111] Sleep disturbances include insomnia, an increase in symptoms of sleep-disordered breathing, circadian rhythm disturbances, excessive daytime sleepiness, abnormal dreams, and the emergence of restless legs syndrome.[112] One study from Wuhan, China observed 1733 patients 6 months after discharge for COVID-19; fatigue or muscle weakness (63%) and sleep difficulties (26%) were the most common persistent concerns,[113] although the physiology of these complaints has not been confirmed. Following the international spread of H1N1 in 2009 and 2010, many patients similarly described new-onset persistent sleepiness. While H1N1 saw a subsequent increase in the number of patients diagnosed with narcolepsy,[47] this same trend has not yet been seen post–COVID-19. While there is no consensus on the physiology or the evaluation and management of patients with postacute COVID-19 syndrome, a careful sleep history and optimization of sleep health is good practice.

Kleine-Levin Syndrome

In contrast to other disorders of hypersomnolence, Kleine-Levin syndrome is episodic, rather than persistent. Clinical features for the syndrome of episodic sleepiness and mood changes in Kleine-Levin syndrome include hypersomnia, varying degrees of hyperphagia, irritability, hypersexuality, cognitive changes,

TABLE 3-6 **Treatment of Cataplexy in Narcolepsy Type 1**

Medication Class	Therapeutic dose (adult)	Adverse effects
Serotonin-norepinephrine reuptake inhibitors		
Venlafaxine	37.5 mg to 325 mg/day	Common: nausea, weight loss, dizziness, headache, constipation, insomnia, somnolence, tremor Rare, serious: suicidal ideation, QT interval prolongation, serotonin syndrome
Selective serotonin reuptake inhibitors		
Fluoxetine	10 mg to 60 mg/day	Common: nausea, insomnia, tremor Rare, serious: suicidal ideation, QT interval prolongation, serotonin syndrome
Sertraline	50 mg to 200 mg/day	
Citalopram	20 mg to 40 mg/day	
Tricyclic antidepressants		
Clomipramine	25 mg to 250 mg/day	Common: dry mouth, constipation, diaphoresis, blurred vision, somnolence, weight gain, orthostatic hypotension Rare, serious: cardiotoxicity, suicidal ideation, bone marrow suppression, QT interval prolongation, serotonin syndrome
Imipramine	75 mg to 200 mg/day	
Protriptyline	15 mg to 40 mg/day in three to four divided doses	

and mood changes. Patients experience recurrent periods of hypersomnia with sleep durations in excess of 18 hours per day.[114] In addition to excessive sleepiness, patients also have at least one of the following symptoms: cognitive dysfunction, derealization, major apathy, or disinhibited behavior (such as hypersexuality or hyperphagia).[1] The most common description of the mood changes with these episodes includes apathy and derealization; hyperphagia and hypersexuality occur less commonly, both in approximately 50% of patients.[114] For diagnosis, patients must have two separate attacks, returning to a normal baseline in between; these episodes last 2 days to 5 weeks and occur at least once every 18 months. Unlike narcolepsy and idiopathic hypersomnia, symptoms of Kleine-Levin syndrome often lessen or resolve over time,[114] typically after about 8 years, but can be debilitating due to limitations on academic and occupational functioning during recurrent episodes.

EPIDEMIOLOGY. The rarest of the central disorders of hypersomnolence, Kleine-Levin syndrome has an estimated prevalence of 1 to 5 cases per 1 million[114] and is typically diagnosed in males age 12 to 20 years.[114]

PATHOPHYSIOLOGY. The etiology of Kleine-Levin syndrome is unknown; although it is typically sporadic, a minority of cases can be familial.[115] Single-photon emission computerized tomography (SPECT) imaging demonstrates abnormalities during and between symptomatic episodes; during active symptoms, hypoperfusion of the right dorsomedial prefrontal cortex and right parietotemporal junction is present, which may correlate with the patient's mood or apathy exhibited during episodes. During asymptomatic periods patients with Kleine-Levin syndrome have hypoperfusion involving the hypothalamus, thalamus, caudate nucleus, and some cortical associative areas compared with controls.[116] Parallels between Kleine-Levin syndrome and bipolar disorder exist, namely, their episodic nature and some shared genetic features. Variants in the *TRANK1* gene have been weakly associated with bipolar disorder (10% increased risk) and these polymorphisms are associated with a 50% increased risk of Kleine-Levin syndrome.[117]

TREATMENT OF KLEINE-LEVIN SYNDROME. Kleine-Levin syndrome is so rare that no clinical trials of therapies exist, and data regarding therapeutic tolerability and efficacy are based on case series. Patients require accommodations so that they can be excused from work and school during hypersomnia bouts due to severe sleepiness, cognitive difficulties, and behavioral dysregulation. Lithium may decrease the frequency, severity, and duration of episodes[118]; the American Academy of Sleep Medicine treatment guidelines include a weak recommendation for lithium in adults with Kleine-Levin syndrome[90] based on limited evidence. During the attacks of sleepiness, a trial of wake-promoting medications can be attempted; amphetamines appear more effective than methylphenidate for excessive sleepiness, but not for the other manifestations of this disorder.[119] In the authors' experience, stimulants are not helpful and can worsen some of the behavioral or psychiatric symptoms of the syndrome. In a cohort study of 108 patients with Kleine-Levin syndrome, investigators reported marginal efficacy for amantadine and mood stabilizers.[120] Other therapies that may shorten episode duration include IV steroids,[121] antiseizure medications (eg, carbamazepine, valproic acid, phenobarbital, phenytoin),[91] and clarithromycin.[90,122]

KEY POINTS

- Following postacute COVID-19 infection, more than half of patients with persistent symptoms describe fatigue and about a quarter of patients with persistent symptoms describe sleep difficulties.
- Clinical features of Kleine-Levin syndrome include episodic sleepiness and mood and behavioral changes (hyperphagia, irritability, hypersexuality, and cognitive changes).
- Most commonly, mood changes during episodes of Kleine-Levin syndrome include apathy and derealization. Hyperphagia and hypersexuality each occur in approximately 50% of patients.
- Lithium may decrease the frequency, severity, and duration of episodes in Kleine-Levin syndrome.

CONCLUSION

Central disorders of hypersomnolence have a significant impact on daily function and optimal participation in school, work, social, and family interactions. Obtaining a detailed clinical sleep history is critical for recognizing these disorders, and thoughtful interpretation of neurophysiologic testing is needed for accurate diagnosis. Tailoring treatment approaches to meet the needs of individuals and account for medical and psychiatric comorbidities is necessary to improve disease burden, daytime function, and quality of life.

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DISCLOSURE

Continued from page 1045

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Obstructive Sleep Apnea

By Karin G. Johnson, MD, FAAN, FAASM

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing. This article describes advances in the diagnosis, testing, treatment, and monitoring of OSA.**

LATEST DEVELOPMENTS: **Home sleep apnea testing and in-laboratory polysomnography are the most commonly used diagnostic tools in the identification and monitoring of OSA, but new methods for diagnosis and at-home monitoring of treatment response are being developed and validated. While the apnea-hypopnea index is regularly used to define OSA severity, recognition is increasing of its inability to risk-stratify patients. Other sleep study data including arousal threshold, hypoxic burden, and pulse rate variability as well as clinical characteristics can help with risk stratification. The most effective treatment is continuous positive airway pressure (CPAP), which can be limited by adherence and tolerance in some patients. Newer masks and comfort features including heated tubing and expiratory pressure relief may improve tolerance to positive airway pressure (PAP) therapy. Additional treatment options include other PAP modalities, mandibular advancement devices, tongue stimulation therapy, negative inspiratory pressure, nasal expiratory pressure valves, nasal congestion treatments, upper airway surgeries including hypoglossal nerve stimulation, and medications.**

ESSENTIAL POINTS: **OSA is a common disorder that causes sleep and daytime symptoms and increases the risk of neurologic and medical complications. Neurologists should be aware of atypical presentations and understand the diagnostic and treatment options.**

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common subtype of sleep-disordered breathing which also includes central sleep apnea syndromes, sleep-related hypoventilation syndromes, sleep-related hypoxemia disorder, snoring, and catathrenia (sleep-related groaning) from prolonged expiration. This article reviews the epidemiology, pathophysiology, clinical presentation, and diagnostic and treatment options of OSA.

DEFINING OBSTRUCTIVE SLEEP APNEA

OSA results from repetitive narrowing or collapse of the upper airway that leads to arousals or intermittent hypoxia. An apnea is defined as the complete or near-complete blockage of airflow as measured by a thermistor for at least

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Dr Johnson discusses the unlabeled/investigational use of acetazolamide, hormone replacement therapy, and montelukast for the treatment of obstructive sleep apnea.

10 seconds.[1] Obstructive apneas involve persistent respiratory effort (FIGURE 4-1A). Partial blockages in the airflow as measured by a pressure transducer are termed hypopneas (FIGURE 4-1B) and, depending on the criteria used, are associated with cortical arousals, at least 3% or 4% oxygen desaturation, or both. Central apneas have an absence of effort throughout the apnea (FIGURE 4-1C), while mixed apneas typically start with an absence of effort followed by effort in the latter part of the apnea (FIGURE 4-1D). Respiratory-related arousals are periods of obstruction, as evidenced by flow limitation or snoring followed by an arousal, that do not meet hypopnea criteria.

Typically, the severity of OSA is determined by the number of obstructive events per hour and is most commonly quantified using the apnea-hypopnea index, which is defined as the number of apneas and hypopneas per hour of sleep. Mild OSA is typically defined by an apnea-hypopnea index score greater than or equal to 5 in the setting of symptoms or significant comorbid conditions,

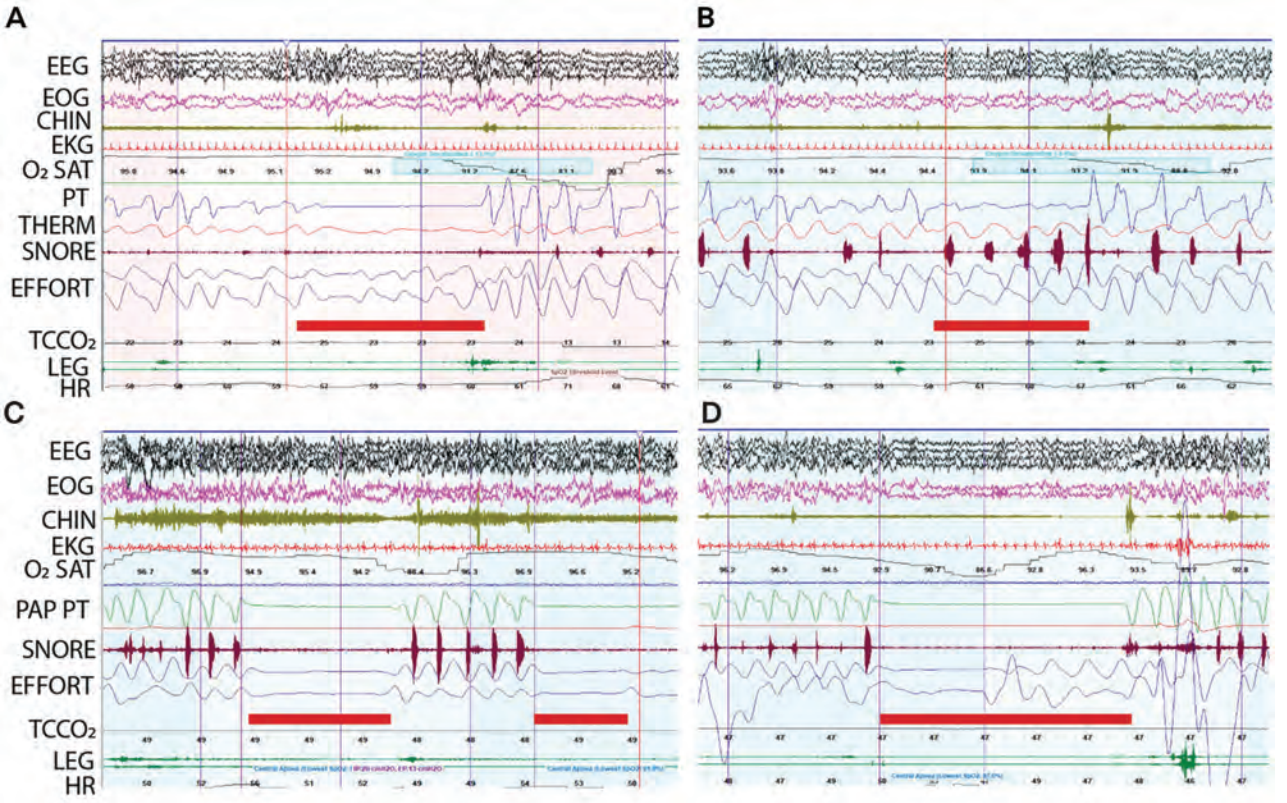

FIGURE 4-1

Scoring of respiratory events on polysomnography. The red bars indicate event duration. *A*, Obstructive apnea with greater than or equal to 90% reduction in thermistor signal (THERM) with persistent effort. *B*, Obstructive hypopnea with greater than 30% reduction in pressure transducer (PT) with greater than or equal to 3% oxygen desaturation or arousal. *C*, Central apnea with greater than or equal to 90% reduction in PT signal with absent effort. *D*, Mixed apnea with greater than or equal to 90% reduction in PT signal with initially absent effort followed by resumption of effort.

CHIN = chin electromyogram; EEG = electroencephalogram; EFFORT = chest and abdomen movement; EKG = electrocardiogram; EOG = electrooculogram; HR: heart rate; LEG = right and left anterior tibialis electromyogram; O_2 SAT = oxygen saturation; PAP PT = pressure transducer measured by positive airway pressure device; SNORE: snore signal; $TCCO_2$ = transcutaneous carbon dioxide.

while moderate and severe OSA correspond to an apnea-hypopnea index score greater than or equal to 15 and 30, respectively. In children, the threshold apnea-hypopnea index score for treatment is typically 1 (or obstructive hypoventilation, defined as PCO_2 >50 mm Hg for >25% of the total sleep time either measured by arterial PCO2 or surrogate),[2] although this is not universally accepted, and the threshold may vary according to the child's age. Hypopneas are typically defined by at least a 30% drop in airflow associated with either an arousal or at least a 3% oxygen desaturation, which is known as AHI3a. The Centers for Medicaid & Medicare Services defines hypopneas as being associated with at least a 4% oxygen desaturation, which is known as AHI4 and is a much stricter criterion.

Other commonly used indexes include the respiratory disturbance index, which is defined by the number of apneas, hypopneas, and respiratory-related arousals per hour of sleep, and the respiratory event index, which refers to the number of apneas and hypopneas per hour of monitoring time. The respiratory event index is typically used for home sleep apnea testing without EEG, and thus total sleep time is unknown. While the same cutoffs for severity are typically used for each index, they may differ greatly within a patient.[3] Index scores may also differ greatly from night to night and can be influenced by body position (eg, typically worse in a supine position), sleep staging (eg, more obstructive events are typically observed during rapid eye movement [REM] sleep), and certain medications or substances, including alcohol or tobacco.

It is increasingly recognized that the apnea-hypopnea index and other indexes are inadequate at predicting which symptomatic patients will respond to treatment[4-7] and do not fully predict cardiovascular risk or death.[8-10] An AHI4 score greater than 15 does tend to correlate more than AHI3a with a higher risk of negative cardiovascular outcomes and death. However, data suggest that even patients with mild OSA with increased heart rate variability and sympathetic response to events such as periodic limb movements may also be at higher risk for additional complications.[11,12] Comorbid insomnia has also been shown to increase cardiovascular risk in patients with moderate to severe OSA.[13] Other polysomnographic features beyond the apnea-hypopnea index like hypopnea duration, degree of flow limitation, and hypoxic burden may also be useful in predicting cardiovascular risk and response to treatment.[14,15] Medicare currently requires the use of the AHI4 criterion so many patients with milder disease do not meet their coverage criteria, which disproportionally affects women due to their increased likelihood of hypopneas with arousals and events only in REM sleep.[3,16]

Some forms of obstructive sleep-disordered breathing do not meet OSA criteria but can be as symptomatic. For example, prolonged partial flow limitation consists of prolonged periods of increased respiratory effort with increased carbon dioxide but without desaturation or arousals, so the apnea-hypopnea index score is often within normal limits.[17] Similarly, patients with upper airway resistance syndrome may have an apnea-hypopnea index score within normal limits, especially if the desaturation criterion is used, because upper airway resistance syndrome involves periods of flow limitation associated with arousals but with stable oxygen saturation.[18] Obesity hypoventilation syndrome is often associated with severe OSA, but hypoventilation can occur out of proportion to the upper airway obstruction and may result from decreased respiratory muscle activity and lower tidal volumes, especially during REM sleep.

KEY POINTS

- Obstructive sleep apnea (OSA) is the most common subtype of sleep-disordered breathing.
- OSA results from repetitive narrowing or collapse of the upper airway that leads to arousals or intermittent hypoxia.
- The severity of OSA is typically determined by the number of events per hour, or the apnea-hypopnea index or respiratory event index.
- The apnea-hypopnea index does not accurately predict treatment response, cardiovascular risk, or death so hypoxic burden, heart rate variability, and flow limitation may help inform risks.

TABLE 4-1[19] reviews some of the physiologic changes and clinical outcomes that can occur in response to obstructive sleep-disordered breathing. The risks of OSA and benefits of treatment vary with age. OSA may provide older patients with a protective benefit against cardiovascular and cerebrovascular events because of ischemic preconditioning, and thus treatment may not have as much of a benefit as it does for younger patients.[20] Treating patients with snoring, mild OSA, or upper airway resistance syndrome pattern to prevent the evolution of disease may be beneficial. Snoring is hypothesized to cause low-frequency

TABLE 4-1 **Physiologic Changes and Clinical Outcomes with Obstructive Sleep Apnea[a]**

Physiologic changes

- Chronic intermittent hypoxia
- Hypercapnia
- Ventilatory overshoot hyperoxia
- Increased sympathetic nervous system activity (increased parasympathetic activity with upper airway resistance syndrome)
- Autonomic nervous system dysregulation
- Sleep fragmentation
- Increased arousals
- Reduced sleep duration
- Snoring vibration
- Intrathoracic pressure changes
- Reduced glymphatic clearance

Intermediate changes

- Increased inflammation
- Increased oxidative free radicals
- Impaired diastolic function
- Decreased cardiac output
- Increased left to right shunting through patent foramen ovale
- Increased atrial natriuretic peptide
- Endovascular damage
- Increased blood pressure
- Increased atherosclerosis (worse in carotid arteries)
- Hypercoagulability (fibrinogen activation)
- Increased heart rate variability
- Cerebrovascular dysregulation
- Upper airway sensory nerve dysfunction
- Reduced genioglossus response to hypoxia
- Increased tau and amyloid protein deposition

CONTINUED ON PAGE 1075

vibrations that can cause traumatic sensory nerve damage in the oropharyngeal and laryngeal regions. This nerve damage can decrease the aryepiglottic reflex and reduce the genioglossus response to hypoxia, which are correlated with higher apnea-hypopnea index scores because more severe events are then needed to trigger upper airway opening and arousals.[21] Endothelial and neurodegenerative changes due to OSA may not be reversible, so treatment should generally be started early. Vascular changes (eg, increased right ventricular afterload, changes in left ventricular afterload, increased transmural

CONTINUED FROM PAGE 1074

Clinical outcomes

- Systemic and pulmonary hypertension
- Neurodegeneration and dementia
- Atherosclerosis
- Congestive heart failure
- Cardiac arrhythmias (eg, atrial fibrillation)
- Stroke and transient ischemic attack
- Insulin resistance and glucose intolerance
- Type 2 diabetes mellitus
- Obesity
- Increased malignancy risk
- Myocardial infarction and stent failure
- Cognitive, memory, and concentration impairments
- Hyperactivity (children)
- Elevated all-cause mortality
- Sudden cardiac death
- Higher rates of motor vehicle accidents
- Increased rates of intracranial hypertension
- Floppy eyelid syndrome
- Migraine and other headache disorders
- Breakthrough seizures
- Polycystic ovarian syndrome
- Preeclampsia and other obstetric complications
- Nocturia
- Insomnia
- Gastroesophageal reflux
- Higher rates of hospital readmission

[a] Modified with permission from Foldvary-Schaefer NR, et al, Continuum.[19] © 2017 American Academy of Neurology.

pressure on left and right ventricles, pulmonary microvascular bed and cerebrovascular degeneration) may lead to short-term effects like left-to-right shunting through a patent foramen ovale[22] or decreased brain perfusion after a stroke,[23] as well as long-term consequences like pulmonary hypertension and heart failure.[24]

OBSTRUCTIVE SLEEP APNEA PRESENTATIONS

Loud or disruptive snoring, witnessed apneas, gasping arousals, and excessive daytime sleepiness are the classic symptoms of OSA, but many patients lack most

TABLE 4-2 **Common Presenting Symptoms of Obstructive Sleep Apnea**[a]

Daytime

- Excessive sleepiness
- Fatigue, exhaustion, or tiredness
- Impaired memory or concentration
- Attention deficit hyperactivity disorder diagnosis or symptoms
- Irritability or anxiety
- Depressed mood
- Morning headaches
- Fibromyalgia
- Unrefreshing sleep
- Difficulty getting up in the morning

Nighttime

- Snoring
- Gasping or choking
- Witnessed apneas
- Insomnia, typically sleep maintenance type
- Restless sleep
- Nightmares
- Nocturia
- Night sweats
- Dry mouth
- Nocturnal gastroesophageal reflux
- Parasomnias

Daytime and nighttime

- Uncontrolled hypertension (lack of nocturnal dipping)
- Atrial fibrillation
- Impaired glucose control

[a] Modified with permission from Foldvary-Schaefer NR, et al, Continuum.[19] © 2017 American Academy of Neurology.

or all of these symptoms. TABLE 4-2[19] summarizes some of the daytime and nighttime symptoms commonly seen in patients with OSA. Restless legs syndrome and parasomnias, including sleepwalking and REM sleep behavior disorder, can be triggered by OSA. While high blood pressure is more common in patients with OSA, nonhypoxic forms of obstructive sleep-disordered breathing like upper airway resistance syndrome and prolonged partial flow limitation may stimulate the parasympathetic system, leading to orthostatic hypotension and cold hands or feet.[21]

Many patients do not report sleep-related or daytime symptoms for several reasons: (1) they lack bed partners to note symptoms, (2) they do not recognize chronic symptoms as problematic until they improve with treatment, (3) they attribute symptoms (eg, nocturia) to other medical conditions or medications, or (4) they are truly asymptomatic. Women are more likely than men to present with atypical symptoms, such as sleep maintenance insomnia and fatigue, and are less likely to be diagnosed and treated for OSA even in the presence of typical symptoms of snoring and daytime sleepiness.[25]

Snoring and sleepiness have also been found to be insensitive for identifying OSA in patients with comorbidities like stroke and heart failure.[26] Screening tools such as the STOP-BANG,[27] STOP-BAG-O,[28] and Berlin questionnaires[29] combine a mix of symptoms and characteristics like sex and body mass index (BMI) and the presence of comorbidities like hypertension, and may be useful for identifying patients with the highest likelihood of severe OSA.[28]

Obesity is commonly associated with OSA, but about 30% of patients with OSA are not obese. A BMI greater than or equal to 28 kg/m^2 is associated with an increased risk of OSA as BMI increases.[30] A neck circumference greater than 43.2 cm (17 in) in men and 40.6 cm (16 in) in women, as well as truncal obesity, can contribute to OSA risk.[31] Tonsillar hypertrophy, adenoid hypertrophy, or both can cause OSA in childhood, but rarely in adulthood. TABLE 4-3[19] summarizes findings that are consistent with a higher risk of upper airway obstruction. Ethnicity and ancestry also influence the physical examination and causal mechanisms associated with OSA.[32] However, more research is needed on the relationships between risk of OSA, ethnicity, and environmental factors such as cultural practices, country of residence, and health care access.[33,34]

Sleeping in a supine position, drinking alcohol, and smoking tobacco can worsen OSA. It is typically thought that sedative medications worsen the severity of OSA due to suppressing arousals needed to prevent worsening desaturations; however, in patients with nonhypoxic OSA, pharmacologic suppression of the arousals may improve sleep apnea severity by reducing the number of postarousal respiratory disturbances. Some patients have worse OSA when sleeping in a lateral position if they have a structural restriction such as from a lobectomy or paralyzed diaphragm affecting the upper lung.

While some studies show that patients with sleep apnea who experience sleepiness have higher rates of cardiovascular disease than patients without sleepiness,[35] asymptomatic or atypically symptomatic patients may still benefit from continuous positive airway pressure (CPAP) therapy, especially if nightly CPAP duration is adequate.[36,37] Underlying conditions such as high blood pressure and atrial fibrillation may improve with OSA treatment in otherwise asymptomatic individuals and factor into decisions regarding ongoing OSA therapy. The decision to treat asymptomatic patients for cardiovascular or cerebrovascular prevention alone is more difficult. Despite suggestive

KEY POINTS

- Women are more likely to present with atypical OSA symptoms including sleep maintenance insomnia and fatigue.
- Obesity is commonly associated with OSA, but about 30% of patients with OSA are not obese.
- Sleeping in a supine position, drinking alcohol, and smoking tobacco can worsen OSA.

observational studies and improvement of intermediate outcomes (eg, hypertension, atherosclerosis, arrhythmias, inflammation and hypercoagulability markers, cerebral blood flow autoregulation) with CPAP treatment, current knowledge remains incomplete.[38] The ability to successfully perform long-term randomized outcome trials in patients with OSA has been limited by multiple factors, including low treatment adherence rates, lack of good sham therapy, the difficulty and expense of performing long-term studies, and ethical challenges of whether to include sleepy patients in randomized trials. Thus, these decisions should be made on a case-by-case basis while considering the severity of OSA, patient age, other risk factors, and patient preferences (CASE 4-1).

Untreated OSA has also been associated with increased prevalence, worsened symptom control, or both in other neurologic disorders, including multiple sclerosis, migraine, epilepsy, idiopathic intracranial hypertension, Alzheimer disease, mild cognitive impairment, and Parkinson disease. For more

TABLE 4-3

Physical Examination Findings that May Increase Risk for Obstructive Sleep Apnea[a]

Body mass index ≥28 kg/m^2

Neck circumference >43.2 cm (17 in) in men and 40.6 cm (16 in) in women

Nasal

- Nasal valve collapse
- Hypertrophied turbinates
- Narrow nose
- Nasal polyps
- Deviated septum

Oral

- Retrognathia
- Overjet (upper teeth protrude diagonally against the lower teeth)
- Malocclusions
- Large, elongated, or swollen uvula
- High-arched and narrow palate
- Low-hanging or elongated soft palate
- Narrow mandible and maxilla
- Lateral scalloping of the tongue
- Macroglossia
- Class 3 or 4 Friedman or Mallampati oral airway patency[b]

[a] Modified with permission from Foldvary-Schaefer NR, et al, Continuum.[19] © 2017 American Academy of Neurology.

[b] Visualization of the base of the uvula and soft palate only (class 3) or hard palate and tongue only (class 4). The Friedman assessment is done with the tongue in a neutral resting position, while the Mallampati assessment is done with the tongue protruded.

information, refer to the article "Sleep Disorders in Patients with Neurologic Disease," by Joyce K. Lee-Iannotti, MD,[39] in this issue of *Continuum*.

TESTING FOR OBSTRUCTIVE SLEEP APNEA

While symptoms, screening questionnaires, or overnight oximetry patterns may predict the presence of OSA and higher risks of adverse outcomes, most insurance companies require limited-channel cardiorespiratory testing or in-laboratory polysomnography to establish a diagnosis and qualify for treatment coverage. TABLE 4-4 summarizes the differences between home sleep apnea testing and in-laboratory polysomnography testing. Most home sleep apnea tests

CASE 4-1

A 49-year-old man with a body mass index of 42 kg/m^2, hypertension, and mildly elevated cholesterol recently experienced a transient ischemic attack. He was referred to a sleep clinic for obstructive sleep apnea (OSA) evaluation as part of a stroke risk factor stratification. He thought that he might snore, but he lived alone. He was skeptical of the possible diagnosis of sleep apnea because he slept 8 hours every night with no awakenings and felt well during the day. His Epworth Sleepiness Scale score was 0/24, which did not suggest daytime sleepiness. He had been in the military and said that he could not tolerate anything covering his face and would never consider continuous positive airway pressure (CPAP) therapy. He reluctantly agreed to a home sleep apnea test, which showed severe OSA. His respiratory event index (apneas and hypopneas with 4% desaturation per hour of test time) score was 54/hour with a lowest oxygen saturation of 76%, and the test recorded 112 minutes with an oxygen saturation less than or equal to 88%.

COMMENT

This case highlights the difficulty of OSA treatment decisions for an asymptomatic individual who is tested for the purpose of screening for cardiovascular or cerebrovascular risk. His severe OSA was likely a strong contributor to both his hypertension and stroke risk. Asymptomatic individuals with OSA can be the hardest to treat, in part because the decision to initiate treatment is difficult if they have no concerns about their sleep or daytime functioning, and because long-term adherence to treatment may be difficult as they may not appreciate any day-to-day symptomatic benefit. Given the severity of the OSA and especially the extent of the hypoxia in this case, treatment was recommended, and CPAP therapy was likely the only action that would fully treat this degree of OSA. Substantial weight loss may have also been curative but would take time, so other treatments would have been recommended as well. If after discussion he was still unwilling to try CPAP therapy, other treatment options like positional therapy, a mandibular advancement device, or bariatric surgery would have been discussed, as partial treatment is better than no treatment. He was not a candidate for OSA treatment with hypoglossal nerve stimulation, which currently is approved for individuals with a body mass index less than or equal to 32 kg/m^2.

include a respiratory effort band around the chest, abdomen, or both, a nasal cannula with a pressure transducer to detect airflow and snoring vibration, and an oximeter to detect pulse and oxygen saturation. Other home sleep apnea testing devices use photoplethysmography to detect peripheral arterial tone along with heart rate, oxygen saturation, movement, body position, snoring, and chest motion. Photoplethysmography, which uses infrared light to measure the volumetric variations of blood circulation, can give information about sleep staging and arousals even in the absence of EEG monitoring.

In-laboratory polysomnography is typically performed as either a whole-night baseline study or a split-night study, which includes a baseline portion that typically lasts for at least 2 hours of recording time (preferably containing a REM period and supine sleep, with the second half of the night involving titration of positive airway pressure [PAP] therapy). Sleep laboratories may have a split-night protocol to start therapy if the patient meets at least a moderate or severe level of sleep apnea in the first hours of the study. The ability to perform split-night studies may be limited, however, if the patient's insurance has only approved a baseline recording. Split-night studies are not typically recommended for children.

Recommendations for home sleep apnea testing have been limited to patients at high risk of moderate to severe OSA[40] given the higher chance of underestimating mild OSA via home sleep apnea testing. However, many patients with mild OSA can still be diagnosed with home sleep apnea testing and insurance often requires home sleep apnea testing for evaluation of uncomplicated OSA; in-laboratory polysomnography is obtained if the home sleep apnea test is unrevealing (CASE 4-2). While guidelines recommend that if central sleep apnea is suspected in-laboratory polysomnography should be ordered, home sleep apnea testing can diagnose central sleep apnea, especially in the presence of a classic Cheyne-Stokes respiration pattern or irregular central apneas in the setting of narcotics. Home sleep apnea testing may be more likely to misinterpret or overcall events, especially with a single effort band or if the patient has frequent arousals. Another reason to start with a polysomnogram

TABLE 4-4 **Comparison of Home Sleep Apnea Testing and Polysomnography**

	Home sleep apnea testing	Polysomnography
Sleep staging	Typically none[a]	Yes
Leg movements	Typically none	Yes
Arousals	Typically none[a]	Yes
Typical sleep routine and substance use[b]	Yes	No
Technician to fix artifacts	No	Yes
Body position assessment	Some	Yes

[a] Peripheral arterial tonography can provide sleep staging and arousal data.
[b] Home sleep apnea testing is typically performed in accordance with the patient's sleep schedule and compared to in-laboratory polysomnography, and the patient is more likely to use substances (eg, nicotine, alcohol, marijuana) that they may not use in the sleep laboratory.

when central sleep apnea is suspected is that treatment optimization for central sleep apnea typically requires in-laboratory titration, so an in-laboratory polysomnography may allow for a split-night study. Polysomnography rather than home sleep apnea testing is recommended for patients with a high risk of central sleep apnea, obesity hypoventilation, comorbid lung disease including chronic obstructive pulmonary disease, comorbid neuromuscular disorders, nonrespiratory sleep disorders including parasomnias, and sleep-related breathing disorders in children.

The main benefits of home sleep apnea testing are its lower cost and the ability for the patient to test in their own home and on their own schedule. These factors may improve the patient's ability to sleep well during testing and may better reflect their nightly sleep, especially if they drink alcohol or use other substances before bed that they may not use in the sleep laboratory. Compared with in-laboratory polysomnography, home sleep apnea tests are more susceptible to artifact, which can lead to uninterpretable data or an overestimation of hypoxia from a faulty oximeter reading. Additionally, if the patient is awake for a long period or if they primarily have respiratory events that cause cortical arousals (rather than oxygen desaturations), the respiratory event index can be underestimated in the absence of EEG monitoring. This underestimation is more likely in women, who often have arousals without desaturations. In addition, Black patients and others with darker skin pigmentation are 3 times more likely to have oximetry underestimate desaturations.[41] Other factors that can affect oximeter accuracy include thick skin, poor circulation, nail polish, and active cigarette smoking. Given that home sleep apnea testing is limited to cardiorespiratory monitoring, it does not assess for loss of REM atonia suggestive of REM sleep behavior disorder, other sleep-related behaviors, or periodic limb movements. Overall, the recommendation is that if there is still a high suspicion for clinically significant sleep apnea or other sleep disorders after a single negative or uninterpretable home sleep apnea test, in-laboratory polysomnography should be performed.[40,41] Depending on the testing modality (in-laboratory polysomnography or home sleep apnea testing) and the hypopnea definition used, there can be wide variation in the incidence and severity of OSA.[3,42]

It is also important to understand that the severity of OSA may be underestimated depending on the type of diagnostic testing used; mild results on home sleep apnea testing should be clinically correlated with data other than the apnea-hypopnea index (eg, hypoxic burden, flow limitation, heart rate variability[43]) that may be helpful in decision making about treatment initiation.

Alternative Diagnostics and Consumer Sleep Apnea Monitoring Technologies

The number of direct-to-consumer technologies available to evaluate OSA has increased in recent years.[45] The most common devices use multiple sensors to determine respiratory event index, position, and sleep stages. Most are based on either oximeters to detect oxygen saturation and pulse including heart rate variability, or photoplethysmography, which can detect changes in blood volume allowing for arterial pulse wave analysis and peripheral arterial tone, providing information about autonomic nervous system response, sleep stage, and arousals. Accelerometers detect motion and body position, which, combined with pulse

KEY POINTS

- Untreated OSA has been associated with increased prevalence, worsened symptom control, or both in many neurologic disorders.
- Home sleep apnea testing can underestimate the severity of OSA, so in-laboratory polysomnography is recommended if home sleep apnea testing results are normal.
- Polysomnography rather than home sleep apnea testing is recommended for patients with a high risk of central sleep apnea, obesity hypoventilation, comorbid lung disease including chronic obstructive pulmonary disease, comorbid neuromuscular disorders, evaluation of nonrespiratory sleep disorders including parasomnias, and sleep-related breathing disorders in children.
- Photoplethysmography can detect changes in blood volume allowing for arterial pulse wave analysis and peripheral arterial tone, which can provide information about autonomic nervous system response, sleep stage, and arousals.

information, is often used to determine sleep staging, typically separated into wake, deep, light, and REM sleep. Some devices also detect snoring, respiratory rate, breathing variance, body temperature, and mandibular movements and use single-lead electrocardiography to evaluate for atrial fibrillation. Many of these devices are designed as rings to wear on a finger at night. Several direct-to-consumer overnight oximetry devices are also available. Finally, several software applications can be used to detect snoring to both gauge risk for OSA and monitor response to OSA treatments.

Currently, these devices are not US Food and Drug Administration (FDA)-approved or insurance-approved for diagnosis but may increase patient awareness and engagement. They may provide real-time feedback that can both encourage patients to seek formal sleep evaluations and alert providers when a treatment is not working well. These devices have the potential to become more meaningful as the number of validation studies increases and they are integrated into electronic health records. The most common risks are data misrepresentation and improper use of data. Additionally, given that these

CASE 4-2

A 54-year-old postmenopausal woman with a body mass index of 29 kg/m^2 reported waking with headaches for the previous 6 months. She had experienced daytime tiredness and unrefreshing sleep for the past 2 years. She went to bed around 10:00 PM and previously could sleep through the night. For the past 2 years she had experienced three or four brief nocturnal awakenings every night, with one or two to use the bathroom. She snored lightly and had no known witnessed apneas or gasping arousals. Her Epworth Sleepiness Scale score was 5/24, which did not suggest excessive daytime sleepiness. Her thyroid-stimulating hormone (TSH) levels were normal.

A home sleep apnea test was performed and her respiratory event index score with 3% oxygen desaturation was in the normal range at 4/hour, with a lowest oxygen saturation of 90%, but the test showed frequent flow limitation and snoring suspicious for possible events with arousals (FIGURE 4-2). She was sent for a follow-up in-laboratory polysomnogram and her AHI3a score was 17/hour with a lowest oxygen saturation of 89%. She was started on auto-adjusting continuous positive airway pressure (CPAP) therapy at a pressure of 7 cm H_2O to 20 cm H_2O and experienced improvement in sleep quality and a reduction in tiredness and headaches.

COMMENT

This case highlights atypical symptoms that are more common in women including sleep maintenance insomnia, fatigue, and headaches. Postmenopause is a typical time for women to present with obstructive sleep apnea (OSA) given the fourfold increase in OSA incidence due to hormonal changes.[44] This case also highlights how home sleep apnea testing can underestimate the severity of OSA, especially in patients with primarily arousals, and the need for a follow-up polysomnogram if there is high suspicion for clinically relevant disease.

devices can generate large amounts of data quickly, the resource utilization required to analyze and document data may outweigh the value added. It is not uncommon for patients using sleep trackers to have anxiety that can then cause worsened sleep quality.[45,46]

TREATMENT

All patients with OSA should be counseled on conservative measures, including nonsupine sleeping positions, nasal congestion therapy, smoking and alcohol cessation, and weight loss. Many patients benefit from treatments including CPAP and other PAP devices, as well as alternative treatments including mandibular advancement devices, hypoglossal nerve stimulation and other surgeries, and pharmacologic treatments.

Positive Airway Pressure Therapy

CPAP is the most effective treatment for OSA in adults. It is essentially a fan connected to a mask that is placed over the nose, mouth, or both and creates a

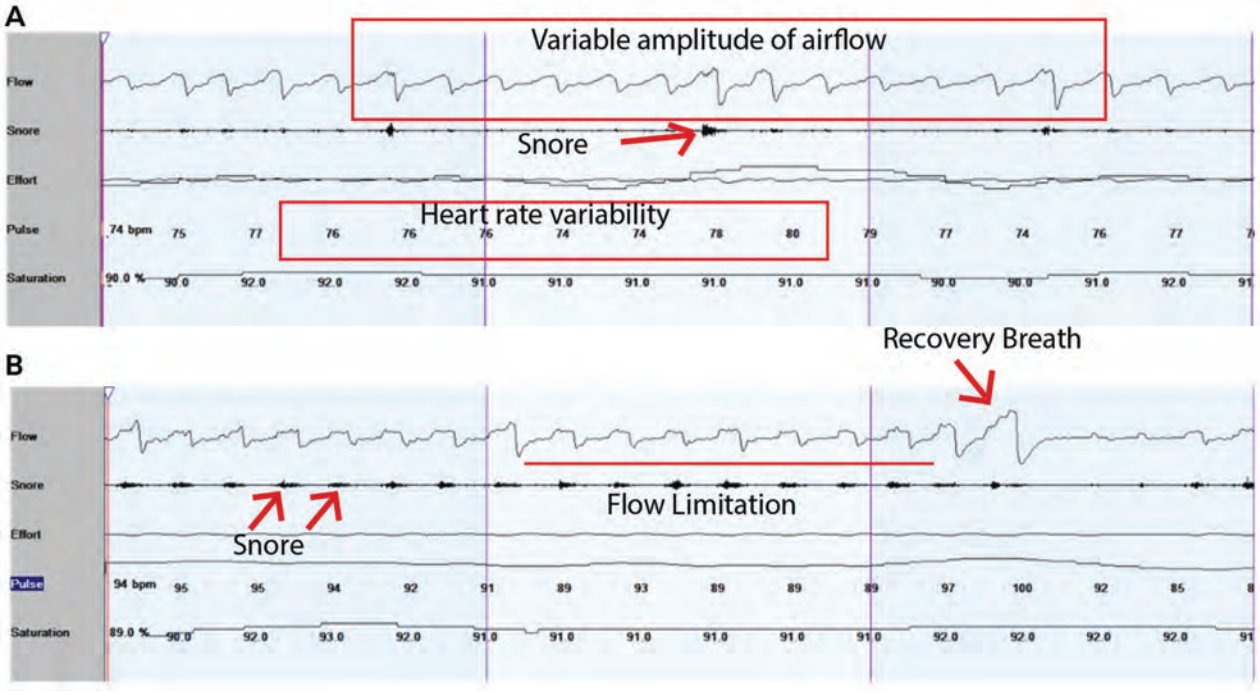

FIGURE 4-2

Home sleep study tracings for the patient in CASE 4-2 showing flow (nasal pressure transducer), snore, effort, pulse, and oxygen saturation. *A*, Flow amplitude changes and snoring and heart rate variability. *B*, Snoring and flow limitation followed by larger recovery breath and heart rate variability. Both may indicate hypopneas with arousals that are unable to be scored without EEG monitoring.

continuous level of air pressure to act as a pneumatic splint and prevent collapse of the upper airway. Most auto-adjusting PAP devices increase the pressure in response to obstructive features such as apneas, hypopneas, snoring, or flow limitation. In the setting of normal breathing and rate, the delivered pressure gradually decreases to the bottom of the pressure range. The sensitivity of pressure changes depends on the specific algorithm a device uses, so not all devices will respond similarly. It is important to note that if the expiratory PAP minimum is set too low, the pressures may not increase to a therapeutic range in time to prevent desaturations or arousals, leading to intolerance or suboptimal response, most often with awakenings 2 to 4 hours into sleep. High mask leak can lead to inadequate treatment response caused by direct disruptions from the leak itself arousing the patient or by subtherapeutic pressure delivery. High mask leak should be addressed, as it can limit the effectiveness and responsiveness of auto-adjusting positive airway pressure therapy. High leak values and a high number of unknown events on the device-estimated apnea-hypopnea index can suggest the need for a mask fitting, the addition of a chin strap, or both (CASE 4-3). Some patients may

CASE 4-3

A 65-year-old man presented to the sleep clinic with excessive daytime sleepiness, loud snoring, witnessed apneas, and four or five awakenings per night to use the bathroom. His body mass index was 34 kg/m^2. A home sleep apnea test showed severe obstructive sleep apnea with a respiratory event index score of 32/hour and a lowest oxygen saturation of 76%. Auto-adjusting positive airway pressure therapy was initiated with a pressure of 7 cm H_2O to 11 cm H_2O, which he started using regularly with a nasal mask. Initial adherence data indicated an average daily use time of 6 hours 51 minutes and his high residual device-estimated apnea-hypopnea index score was 9.8/hour; the patient still felt sleepy during the day. Given the high number of unknown apnea events, a high mask leak was suspected, and a mask fitting was ordered (FIGURE 4-3).

Follow-up adherence data showed that the leak had resolved and the patient's residual device-estimated apnea-hypopnea index score decreased to 2.3/hour with 1.6 obstructive apneas, 0.3 central apneas, and 0.4 hypopneas. The median delivered pressure was 10.6 cm H_2O and the 95th percentile pressure was 10.9 cm H_2O. The patient still felt sleepy during the day and was still waking about every 2 hours at night to use the bathroom. The pressure was changed to 11 cm H_2O to 20 cm H_2O and his residual device-estimated apnea-hypopnea index score on follow-up was 2.0; he then slept well through the night with a single awakening per night and his daytime symptoms were greatly improved.

COMMENT

This case highlights the use of both clinical history and adherence data to manage continuous positive airway pressure (CPAP) follow-up. The resolution of mask leak led to an improvement of the device-estimated apnea-hypopnea index score to the desired range, but the patient remained symptomatic. The pressures were often at the high end of the prescribed range suggesting higher pressures may improve his symptoms.

have high leak due to facial hair, facial anatomy, or a high prescribed pressure level, but if it is not bothering the patient, affecting the duration of use, or causing suboptimal pressure delivery it may not be necessary to address.

Some patients require other forms of PAP therapy that alternate between higher pressure on inhalation and lower pressure on exhalation, which can be used for comfort, to help stabilize breathing, or to ensure a stable level of ventilation. These modalities include bilevel PAP, adaptive servoventilation (a proprietary algorithm), or volume-assured pressure support; the latter two modalities use devices that deliver backup breaths at a set or automatically adjusting rate. Servoventilation may be particularly useful for patients with a periodic breathing pattern, and volume-assured pressure support helps ensure stable ventilation regardless of body position or sleep stage, which can improve the treatment of hypoventilation in patients with neuromuscular disorders or other forms of restrictive lung disease.[47]

Many PAP devices can collect adherence data, which can be used to monitor use and efficacy and troubleshoot comfort issues. Any clinician can request

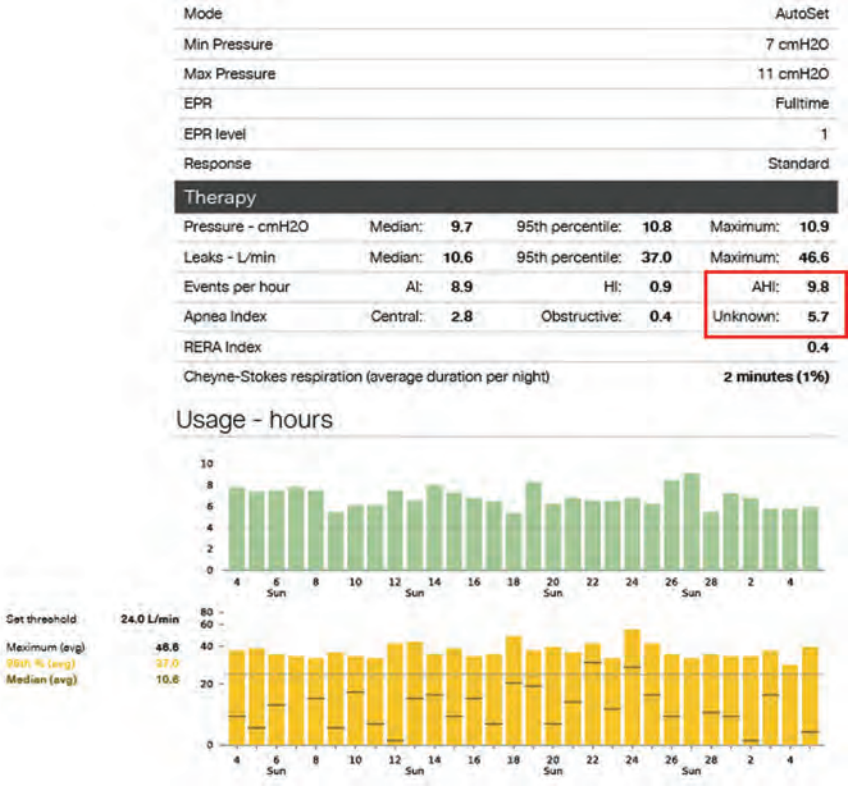

FIGURE 4-3

Initial adherence data for the patient in CASE 4-3, showing a high residual apnea-hypopnea index (AHI) score with a high unknown apnea index consistent with high leak. The AHI score is the sum of the apnea index (AI) and hypopnea index (HI).

EPR = exhalation pressure relief; RERA = respiratory effort–related arousal.

access to cloud-based PAP adherence data, which become available once a patient establishes care with a durable medical equipment company. Adherence data, which often can be followed remotely, can assist with troubleshooting intolerance and identifying suboptimal treatment response. The device-estimated apnea-hypopnea index score is determined by airflow amplitude only when the patient is using the device; some patients with a low device-estimated apnea-hypopnea index score may be undertreated, and pressure adjustments should be considered in persistently symptomatic patients. Additional information including oxygen saturation, device-estimated tidal volume and minute ventilation, arterial blood gas, serum bicarbonate levels, or home carbon dioxide monitoring can help assess hypoventilation and determine if further evaluation or testing is needed to optimize therapy.

Patient-facing applications from PAP device manufacturers can give patients direct feedback on their use as well as information to help with troubleshooting.

CASE 4-4

A 35-year-old woman with anxiety, hypertension, a body mass index of 28 kg/m^2, and obstructive sleep apnea (OSA) (respiratory event index score of 16/hour, worse in the supine position, and a lowest oxygen saturation of 85% on home sleep apnea testing) presented with difficulty tolerating continuous positive airway pressure (CPAP). She snored loudly, especially when sleeping on her back, and slept through the night but woke unrefreshed and was tired throughout the day. Her Epworth Sleepiness Scale score was 8/24, which did not suggest excessive daytime sleepiness. She had difficulty concentrating at work, leading to a warning from her boss. She often had nasal congestion. She tried to use auto-adjusting positive airway pressure (PAP) therapy for 3 months with a nasal pillow and both nasal and full-face masks. She had difficulty falling asleep with CPAP and felt that mask discomfort disrupted her sleep. When she was able to sleep through the night with CPAP, she did feel more alert the next day. CPAP was discontinued and replaced by a combination of nasal congestion treatments, a mandibular advancement device, and avoiding sleeping on her back. She slept better, felt better during the day, and was able to stop using a blood pressure medication. Follow-up home sleep apnea testing with treatment showed a respiratory event index score of 7/hour and a lowest oxygen saturation of 90%.

COMMENT

This case highlights other treatment options in the setting of CPAP intolerance. If response to auto-adjusting positive airway pressure therapy is suboptimal, an in-laboratory titration study should be done to optimize treatment settings and mask fit; however, many patients with disrupted sleep from CPAP would rather pursue alternative therapies. Several features increased this patient's likelihood to respond favorably to non-PAP therapies: a nonobese body mass index, lower OSA severity and degree of oxygen desaturation, symptomatic response to PAP therapy when able to use it, and positional worsening of OSA.

Web-based mask-fitting applications can assist with determining the best mask for a patient.

Treatment of Obstructive Sleep Apnea in Children

Tonsillectomy and adenoidectomy are generally the most effective OSA treatments in children with adenotonsillar hypertrophy.[48] Adenotonsillar tissue is at its largest between ages 3 and 6 years, and as children age this may become less likely to cause OSA. Children with OSA may be more likely to have craniofacial abnormalities such as midfacial hypoplasia, retrognathia or micrognathia, nasal-septum obstruction, or macroglossia that may benefit from surgical treatments, orthodontic treatments, or both to open the upper airway. Nasal congestion should be treated if present. As in adults, obesity is a major risk factor in adolescents, with each 1 kg/m^2 increment in BMI above the 50th percentile being associated with a 12% increased risk for OSA.[49] Weight loss, including with bariatric surgery, is often the best treatment for these patients but PAP therapy may be needed.[50] Facial development needs to be followed in younger children using masks, and airway pressures may need adjustment over time. Like adults, PAP adherence can be challenging.

Alternative Treatments

For most patients, CPAP or other PAP therapy is more likely to resolve obstruction than most nonsurgical alternative treatments. It is important when evaluating a patient for whom CPAP has already failed to determine why and whether another attempt is warranted as many people can be successful on a second try, especially if working closely with a sleeping specialist and with newer mask styles. However, many patients either cannot tolerate CPAP, do not want to use it, or have situations like frequent travel or camping that make it difficult to use. Some patients want alternative treatments for everyday use and others require it only intermittently when CPAP is not an option. Some treatments can be used in combination with CPAP, such as a mandibular advancement device to allow for lower CPAP pressure or to hold a nasal pillow mask in place without straps.

Every patient with obstructive sleep apnea should be counseled on the effects of position (for most patients, a nonsupine sleeping position is recommended), weight loss if overweight, and avoidance of alcohol, sedative medications, and tobacco smoking, especially near bedtime. Addressing healthy sleep habits like sleeping in a cool, dark room, avoiding electronics and clock watching, and having a wind-down routine is also important to increase the likeliness of adherence to and benefit from the chosen therapy.

Adjunctive treatment of nasal congestion can lead to partial improvement of OSA, facilitate the use of PAP therapy, or both. Nasal corticosteroids can be used preventatively, and medications like ipratropium or azelastine can unclog nasal passages at night. Otolaryngology, maxillofacial surgery, or allergy consultations should be considered for patients who require OSA treatment and have refractory OSA symptoms, atypical craniofacial findings, or low or normal BMI who need to be evaluated for other causes of obstruction.

Oral appliance therapies, including mandibular advancement devices, are a common non-PAP therapy that may be covered by medical insurance (CASE 4-4). Mandibular advancement devices protrude the lower jaw and may effectively treat mild to moderate supine-dominant OSA, especially in patients with low or normal BMI. In patients with severe OSA who are unable to tolerate CPAP, a partial

KEY POINTS

- Direct-to-consumer sleep and oxygen monitoring devices may increase patient awareness and engagement regarding sleep health.
- All patients with OSA should be counseled on conservative measures, including nonsupine sleeping positions, nasal congestion therapy, smoking and alcohol cessation, and weight loss.
- Continuous positive airway pressure (CPAP) therapy acts as a pneumatic splint and prevents collapse of the upper airway.
- Auto-adjusting positive airway pressure devices increase the delivered pressure in response to obstructive features such as apneas, hypopneas, snoring, or flow limitation and reduce the delivered pressure in response to normal breathing.
- High mask leak can lead to inadequate treatment response either to direct disruptions from the leak itself arousing the patient or from subtherapeutic pressure delivery.
- Bilevel positive airway pressure, adaptive servoventilation, and volume-assured pressure support may be needed for comfort, to stabilize breathing, or to ensure a stable level of ventilation.
- Adherence data, which can often be followed remotely, can assist with troubleshooting intolerance and identifying suboptimal treatment response.

response with a mandibular advancement device may be better than no treatment. Custom-made oral appliances are more efficacious and comfortable than temporary devices used to estimate treatment response. Some patients do not tolerate a mandibular advancement device due to jaw pain or discomfort from having a device in their mouth during sleep.

Other devices that are not typically covered by insurance include nasal expiratory positive airway pressure devices, which provide partial resistance upon breathing out, leading to a low level of expiratory positive airway pressure that may improve or resolve mild OSA and snoring. Oral negative pressure pulls the tongue and associated structures forward to lessen obstruction. Daytime tongue electrical stimulation works by strengthening tongue muscles, making the tongue less likely to collapse at night, and is authorized in the United States for the treatment of snoring and mild OSA and in Canada for the treatment of mild to moderate OSA.[51] This is similar to how playing the didgeridoo or other myofunctional therapies are felt to improve OSA in some patients, although the level of evidence is low for these other modalities.[52]

Unilateral hypoglossal nerve stimulation is approved for use in adult patients with a BMI less than or equal to 32 kg/m^2, an apnea-hypopnea index score between 15 and 65 events per hour, less than 25% central apneas, an inability to use CPAP, and demonstrated anterior-posterior collapse on a drug-induced sleep endoscopy.[53] After activation of the device with a remote control, a lead in the chest wall senses the effort to breathe through respiratory muscle activation and stimulates branches of the hypoglossal nerve that push the tongue forward. Small studies have been successful in patients with Down syndrome[54]; whether it can be used in individuals with a BMI greater than 32 kg/m^2 is being evaluated. A bilateral hypoglossal nerve stimulator was found to be more successful in patients with concentric palatal collapse.[55]

Several pharmacotherapies have demonstrated an ability to reduce apnea-hypopnea index scores.[56,57] Hormone replacement therapy, especially with both progesterone and estrogen, was shown to reduce the prevalence of OSA in postmenopausal women, but treatment trials have been inconclusive. Carbonic anhydrase inhibitors (eg, acetazolamide) reduce loop gain that drives recurrent events after initial upper airway obstruction and may particularly help patients with periodic breathing or in the treatment of emergent central sleep apnea. Several studies found that donepezil was beneficial for OSA treatment, while others did not.[56] The combination of reboxetine (an antidepressant) and hyoscine butylbromide (an antispasmodic) reduced apnea-hypopnea index scores in a small study. Of note, reboxetine is currently not available in the United States. REM-suppressant medications, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, can reduce REM-related respiratory events. The leukotriene antagonist montelukast has been shown to reduce the respiratory disturbance index and adenoid size in children. Hypothyroidism reduces ventilatory drive, so thyroid replacement therapy in patients with hypothyroidism can improve OSA. While small, short-duration studies suggest that marijuana may help OSA, an American Academy of Sleep Medicine position statement in 2020 recommended against the use of medical cannabis and synthetic marijuana extracts for OSA treatment due to a lack of sufficient evidence of safety and efficacy.[58] Emerging data on pharmacologic treatments for OSA may allow for expanded therapeutic options in the future.

CONCLUSION

OSA often presents with atypical symptoms including insomnia, headaches, cognitive complaints, and nocturia so a high degree of suspicion is necessary. Portable home diagnostic testing allows for a less expensive and more comfortable testing option for many patients, but it has limitations. Additionally, diagnostic scoring with the apnea-hypopnea index may not provide a full risk picture, and other sleep study data including oxygen levels and heart rate variability may help with treatment decisions. CPAP therapy remains the most effective treatment for many patients and appropriate follow-up and use of device data allows many patients to avoid in-laboratory testing, improve adherence rates, and optimize therapy. An increasing number of alternative therapies should be considered in patients who do not want or tolerate PAP. The role of smaller, new home monitoring devices in diagnosis and ongoing management is still uncertain.

KEY POINTS

- **Tonsillectomy and adenoidectomy are generally the most effective OSA treatments in children.**
- **Alternative treatments for OSA include weight loss, positional therapy, mandibular advancement devices, nasal congestion treatments, and unilateral hypoglossal nerve stimulation and other airway surgeries.**
- **Pharmacotherapies including carbonic anhydrase inhibitors, reboxetine, and hyoscine butylbromide may decrease some patients' apnea-hypopnea index scores.**

USEFUL WEBSITES

MY APNEA
A wealth of information, resources, and forums on sleep apnea, maintained by a large network of patients, doctors, and researchers.

myapnea.org

HEALTHY SLEEP
Videos, essays, activities, and resources for a general audience on the importance and science of sleep maintained by the Division of Sleep Medicine at Harvard Medical School and WGBH Medical Foundation.

sleep.hms.harvard.edu/education-training/public-education/sleep-and-health-education-program/sleep-health-education-40

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

VIDEO CONTENT AVAILABLE ONLINE

REM Sleep Behavior Disorder and Other REM Parasomnias

By Roneil Malkani, MD, MS

ABSTRACT

OBJECTIVE: **This article reviews rapid eye movement (REM) sleep behavior disorder (RBD) and other REM sleep parasomnias, particularly recurrent isolated sleep paralysis and nightmare disorder.**

LATEST DEVELOPMENTS: **People with RBD have dream enactment behaviors that can be distressing and cause injuries to themselves or a bed partner. Diagnosis of RBD still requires video polysomnography but new evaluative techniques are emerging. Automatic scoring of REM sleep without atonia, the polysomnographic RBD feature, has led to clearer diagnostic cutoff values. Isolated RBD is strongly linked with neurodegenerative disorders, particularly α-synucleinopathies, with a median latency to neurodegenerative disease diagnosis of 8 years. Mounting imaging, electrophysiologic, and pathologic evidence supports neurodegenerative changes in patients with isolated RBD. Safety precautions should be reviewed with patients to reduce the risk of injury. Clonazepam and melatonin are first-line agents for RBD symptoms, and rivastigmine appears to be beneficial for RBD in people with mild cognitive impairment. For nightmare disorder, image rehearsal therapy is effective and can be delivered through online platforms.**

ESSENTIAL POINTS: **While RBD symptoms can often be managed, patients with isolated RBD should be monitored for signs and symptoms of impending neurodegenerative disease. Individuals who wish to know about the associated risk should be counseled accordingly to allow planning and involvement in research if they choose. Exercise may have some neuroprotective effects, although no treatment has been shown to modify the neurodegenerative risk.**

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RELATIONSHIP DISCLOSURE:
Dr Malkani has received research support from the National Institutes of Health (NIH) and Northwestern University.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Malkani discusses multiple medications and therapies for the treatment of rapid eye movement sleep behavior disorder, none of which are approved by the US Food and Drug Administration (FDA).

INTRODUCTION

Several parasomnias arise in rapid eye movement (REM) sleep. These include REM sleep behavior disorder (RBD), sleep paralysis, and nightmares, which can occur in isolation or in association with various disorders.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

Sleep is behaviorally characterized by motor quiescence. While people dream in REM sleep the body has little to no movement. This paralysis, which spares

extraocular muscles and the diaphragm, is a protective mechanism that has presumably evolved to keep people safe from injuries. When this protective system malfunctions, the dreams can manifest with behaviors; this is known as RBD. Symptoms of RBD were noted in people with Parkinson disease in James Parkinson's essay,[1] and the disorder was identified and named RBD in 1986 by Carlos Schenck and Mark Mahowald.[2] Soon thereafter a strong association was discovered between isolated RBD and the development of neurologic diseases, particularly α-synucleinopathies such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.[3] This finding of prodromal α-synucleinopathy has motivated research aimed at understanding the pathophysiologic links between RBD and neurodegeneration, the prediction of neurodegeneration risk, biomarker identification, and preparation to test potential neuroprotective strategies to delay or prevent the development of neurodegenerative disease.

Clinical Features

REM sleep is characterized by rapid eye movements, a desynchronized mixed alpha and theta EEG background rhythm, and muscle atonia. In addition, REM sleep is typically associated with dreaming. Dysfunction of the underlying neurophysiology of REM sleep, particularly of the mechanisms that control the REM atonia, results in increased motor activity and manifests with dream enactment behaviors.

The *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*) diagnostic criteria for RBD are shown in TABLE 5-1.[4] All criteria must be present to make a diagnosis of definite RBD.[4] Patients must have dream enactment behaviors by history or video polysomnography and REM sleep without atonia (RWA), a polysomnographic finding of increased motor activity during REM sleep. When the history is typical for RBD but video polysomnography is not obtained or limited (eg, due to lack of REM sleep during the study), this clinical entity may be called probable RBD.

A detailed history is essential to characterize a patient's symptoms of RBD, including dreams or nightmares, motor activity, and injuries. Symptom onset often predates the time of presentation by many years. Most people with RBD recall at least some unpleasant dreams. The types of dreams described are often

***ICSD-3-TR* Diagnostic Criteria for REM Sleep Behavior Disorder[a]** TABLE 5-1

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria A through D must be met for a rapid eye movement (REM) sleep behavior disorder diagnosis:**

A Repeated episodes of sleep-related vocalization or complex motor behaviors

B These behaviors are documented by polysomnography to occur during REM sleep or, based on the clinical history of dream enactment, are presumed to occur during REM sleep

C Polysomnographic recording demonstrates REM sleep without atonia

D The disturbance is not better explained by another current sleep disorder or mental disorder

[a] Reprinted with permission from American Academy of Sleep Medicine.[4] © 2023 American Academy Of Sleep Medicine.

persecutory, with the patient defending oneself, being chased by an assailant or animal, or arguing with someone. Less distressing dreams can also be action-packed (eg, playing sports) or calm and enjoyable (eg, playing cards).[5]

Various dream enactment behaviors that have been described include talking, screaming, punching, kicking, throttling, or jumping out of bed (VIDEO 5-1). While these types of behaviors are more commonly reported by patients and bed partners, especially when they are injurious, patients often have simple or noninjurious behaviors that are not observed or reported. Reported event frequency can vary widely, from less than once monthly to even daily, and can vary throughout the course of the disorder. As many as 44% of patients are unaware of the behaviors, so collateral history or recordings are important to estimate the frequency of all dream enactment events, not only those that lead to injury or fall.[5] Furthermore, one study reported that in 11% of patients, RBD symptoms were not volunteered but were elicited with specific questioning.[5] Of note, major or more injurious behaviors, which are more likely to be reported, constitute only a small fraction of the total event number when mild events are taken into account.[6]

A major concern about dream enactment behavior is the risk of injury to patients and their bed partners. Affected individuals may punch or kick the wall or jump out of bed, which can lead to bruises or hip or head injuries. Injuries have been reported in 32% to 76% of patients and 17% to 64% of bed partners.[6] Because of the risk to the bed partner, the patient and bed partner often either put a barrier between them in the bed or sleep in separate beds.

Mood disruption, including depression and anxiety symptoms, are more common in people with RBD compared with controls.[7] In addition, several antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can exacerbate RBD symptoms, so appropriate treatment options need to be carefully considered in patients with RBD.

Several features in the history distinguish RBD from non-REM parasomnias. Non-REM parasomnia events are more common in the first half of the sleep period (particularly during the first hour), and during the event the eyes are often open and the person can respond to the environment, albeit inappropriately. The non-REM parasomnia sleepwalking can include moving away from the bed or out of the room. Attempts to wake a person while sleepwalking can cause them to have an inappropriate or aggressive response. In contrast, dream enactment in RBD can happen across the night but tends to occur in the last half of the sleep period, which is usually richer in REM sleep. People with narcolepsy, who have frequent REM sleep intrusions during wake and sleep, can have dream enactment events at any time in the sleep period. RBD events are related to the internal dream mentation; a patient's eyes are typically closed during these events and they have no awareness of the environment. The lack of atonia is intermittent, and patients may sit up briefly or jump out of bed but do not step out of bed. Patients can wake up easily from RBD behaviors by themselves or from interacting with an observer. While the types of behaviors seen in RBD and non-REM parasomnias appear distinct, these historical details may not be available, and polysomnography can help distinguish these features. When both types of parasomnias co-occur, this is called parasomnia overlap disorder.[4]

Polysomnography Features

In addition to the detection of RWA, as detailed below, video polysomnography is important to evaluate for other sleep disorders such as sleep-disordered breathing, periodic limb movements of sleep, or other non-REM motor events, particularly in people with neurodegenerative disease.[8] Periodic limb movements of sleep are present in about one-half of patients with RBD, more so in those with neurodegenerative disease,[9] and sleep apnea is seen in about one-quarter of people with neurodegenerative disease.[5]

Dream enactment behaviors can be observed on video polysomnography but are not always present during the sleep study. Most events are simple jerks, and less commonly are complex behaviors followed by major and violent movements. Violent movements occur less than 1% of the time. Upper limb movements are more common than leg or head movements.[6]

RWA is the core polysomnographic feature of RBD (FIGURE 5-1) and is required for diagnosis.[4] The American Academy of Sleep Medicine Scoring Manual defines visual scoring of RWA on an epoch of REM sleep based on the presence of tonic (sustained) or phasic (transient) EMG muscle activity.[10] For phasic muscle activity, a 30-second epoch is divided into ten 3-second mini-epochs, and RWA is present if at least 50% of the mini-epochs have bursts of activity (0.1 to 5.0 seconds in duration, at least double the baseline EMG amplitude). The scoring of RWA during any epoch is done based on the presence of any of the following: excessive tonic chin EMG activity (≥50% of the epoch), excessive phasic chin or limb EMG activity (≥50% of the mini-epochs), or if 50% or more of the mini-epochs have either tonic or phasic chin or limb EMG activity. Upper limb EMG may also be used, utilizing either the flexor digitorum superficialis or extensor digitorum communis. While specific criteria exist for scoring a single epoch as having RWA, neither the American Academy of Sleep Medicine Scoring Manual nor the *ICSD-3-TR* defines how many epochs are needed to establish that a patient has RWA for the diagnosis of RBD. However, RWA for RBD diagnosis should not be made based on the presence of only a single epoch with RWA.

Other validated visual scoring methods include the "Montreal" method by Lapierre and Montplaisir, the Sleep Innsbruck Barcelona (SINBAR) criteria, and the Mayo criteria.[11] All sets of criteria rely on a combination of phasic and tonic EMG activity, with slight differences in duration criteria for phasic EMG elevation. The SINBAR criteria include bilateral flexor digitorum superficialis EMG, while the others rely on chin and tibialis anterior EMG electrodes. Upper limb EMG does appear to be important given that movements are more common in arms than legs[6] and chin EMG may have artifacts from sleep apnea.[12] Based on the SINBAR criteria, a cutoff of 32% of REM sleep with RWA using chin and flexor digitorum superficialis EMG was optimal for a diagnosis of RBD.[13] The International RBD Study Group also recommended guidelines on video polysomnography technical settings, REM sleep scoring, RWA scoring, audio and video analyses, and RWA thresholds for RBD diagnosis.[12]

Several automated scoring methods have been developed,[14,15] although it remains unclear if one method is more optimal than another. Currently, their use is mainly limited to research, and they are not widely used in clinical practice.[15] The most widely reported method is the REM atonia index, which is a proportion calculated using automated analysis and ranges from 0 to 1, with higher values indicating more atonia (a REM atonia index score of 1 indicates complete atonia).

KEY POINTS

- Diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) requires historical or video polysomnographic evidence of dream enactment behaviors and REM sleep without atonia.
- Dream enactment behaviors in RBD can include punching, kicking, or falling from the bed, which can cause injuries to the patient and bed partner.
- Dream enactment in RBD can happen across the night but tends to occur in the last half of the sleep period, which is usually richer in REM sleep.
- Polysomnography is important to evaluate for RBD mimics, such as sleep apnea or periodic limb movements of sleep.

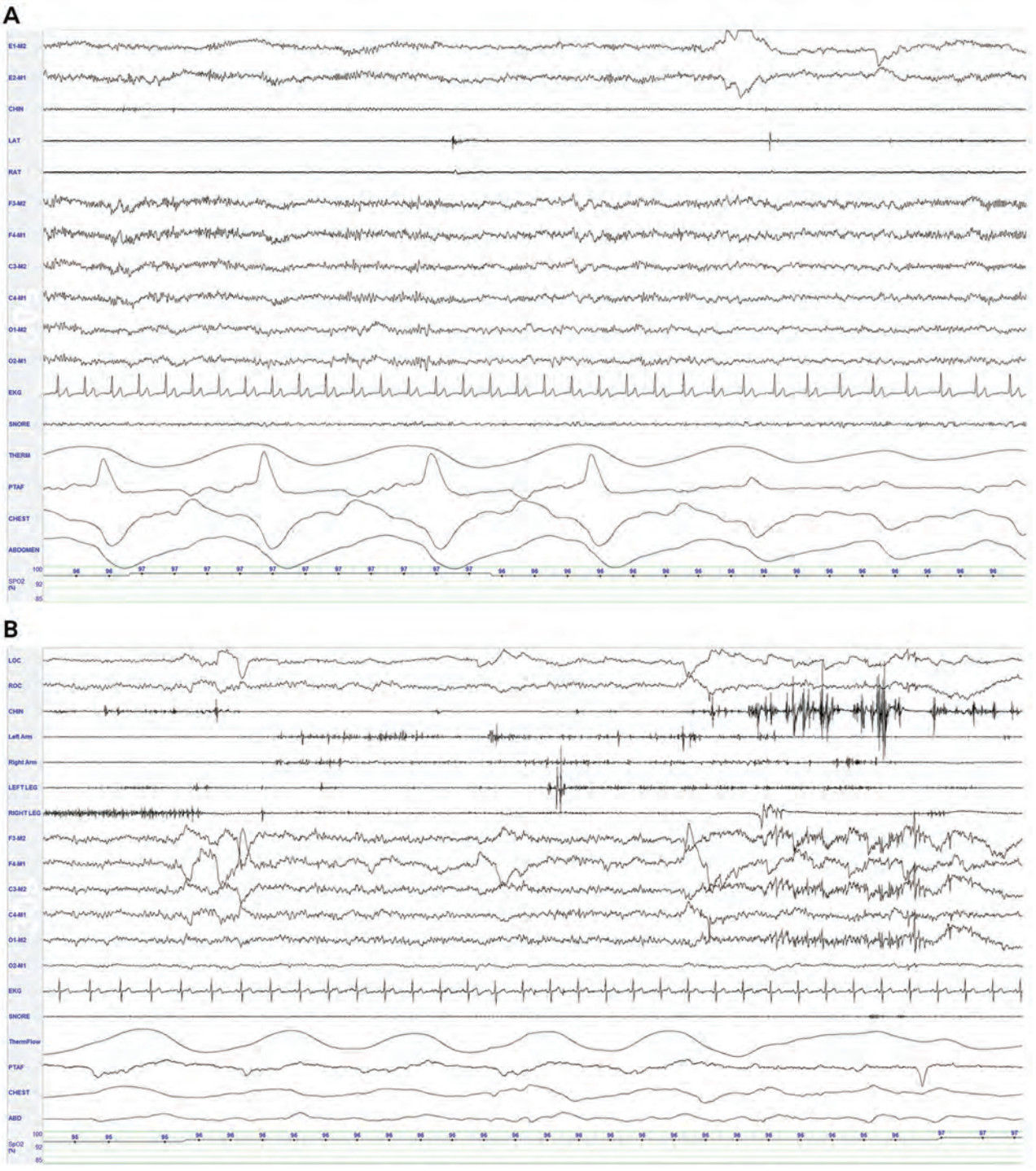

FIGURE 5-1
Polysomnograms showing rapid eye movement (REM) sleep with and without atonia. *A*, 30-second epoch of normal REM sleep. Channel names are on the left side. Note the low EMG tone in the CHIN and limb (left anterior tibialis [LAT], right anterior tibialis [RAT]) EMG electrodes. *B*, 30-second epoch of stage REM sleep in a patient with REM sleep behavior disorder. Note the increased motor activity throughout the epoch with some tonic activity in the right leg electrode and phasic activity in the chin and left and right arm electrodes.

A REM atonia index score less than 0.8 is considered abnormal; this cutoff has been validated in isolated RBD and RBD associated with Parkinson disease and correlates well with visual RWA scoring methods. Automated RWA scoring methods still require human supervision for REM sleep scoring and artifact exclusion.

Video polysomnography is necessary for the diagnosis of RBD, although the sensitivity of the test is not perfect. Reasons include night-to-night variability in the occurrence of RBD events and RWA, lack of REM sleep during the night of the study, or artifacts that obscure the detection of RWA. In cases with no observed REM sleep on the video polysomnogram, severe obstructive sleep apnea, which can mimic RBD, is common and should be addressed prior to reevaluation. Sleep disruptions and unpleasant dreams due to sleep apnea–related arousals can be very similar to those of RBD.[16] In addition, α-synucleinopathies can also result in a lack of REM sleep.[17]

KEY POINT

- Questionnaires can aid in RBD screening but have high false-positive rates compared to polysomnography-confirmed RBD diagnosis.

Questionnaires

Given the time and financial cost of video polysomnography, several questionnaires and scales have been developed and validated against polysomnography.[18] Questionnaires intended for diagnostic purposes have limitations due to recall bias; up to 44% do not recall RBD behaviors in sleep, and collateral history may not be available.[5] Furthermore, these questionnaires cannot distinguish RBD from RBD mimics. Other scales are intended to monitor RBD severity longitudinally. The RBD Screening Questionnaire is a self-administered scale that measures the presence or absence of RBD symptoms over one's lifetime.[18] This scale is validated in the sleep clinic population and can be used for screening or diagnosis but not disease monitoring. The Mayo Sleep Questionnaire has a screening question that, if positive, triggers five additional questions and is validated for RBD screening in patients with neurodegenerative disease but not isolated RBD.[18] The Innsbruck RBD Inventory is a five-question survey validated in a sleep center that distinguishes RBD from other disorders and can be used for screening or diagnosis.[19] The RBD Questionnaire-Hong Kong evaluates behavior and dream frequencies and can be used for disease monitoring.[18] However, it cannot differentiate between subtypes of RBD (isolated or secondary) or RBD from non-REM parasomnia; of note, this scale has not been validated in English. The RBD Single-Question Screen is a single-question survey that assesses for any history of dream enactment behaviors.[18] The simple design is meant for screening the general population with minimal questionnaire burden but was validated in a sleep clinic population, not the general population.[18]

The recognized limitations of questionnaires and video polysomnography highlight the need for more practical diagnostic and surveillance techniques. Wrist actigraphy may be useful with high sensitivity and moderate to high specificity, but only with expert review.[20] Other automated analyses using minimal sensor recordings with electrooculogram and overnight EMG have shown moderate agreement for sleep staging and high agreement for RBD detection compared with visual scoring on video polysomnography.[14]

Epidemiology

Isolated RBD typically starts in the fifth or sixth decade of life with a mean age of estimated onset of 63 years and a mean age at diagnosis of 68 years.[5] RBD due to

narcolepsy, however, often starts at a younger age. In those over 50 years old, RBD is more common in men but may be underreported in women. One cohort with video polysomnography–confirmed RBD was 82% male.[21] Men and women under 50 years old are affected equally.[22] Risk factors for RBD have varied among studies but are shared with those linked to the development of α-synucleinopathies, including pesticide exposure, smoking, and head injury.[22]

Several studies have examined the prevalence of isolated RBD with varying results, possibly due to methodologic differences. The prevalence of video polysomnography–confirmed (definite) RBD is 0.68% (range 0.29% to 1.15%), while studies of probable RBD report a much higher prevalence of 5.65%. The discrepancy between definite and probable RBD prevalence likely results from the high false-positive rate seen with the questionnaires; this lack of accuracy can be mitigated by follow-up clinical evaluation or a telephone interview.[23]

Gene studies demonstrate that variants in glucocerebrosidase (*GBA*) confer an increased risk of isolated RBD and Parkinson disease. *GBA* mutations are seen more commonly in people with isolated RBD (9.5%) compared with those without RBD (4.1%). The more severe the variant, the greater the association between isolated RBD and Parkinson disease and the earlier the age of Parkinson disease development.[24] Other implicated genes include synuclein genes and genes related to circadian rhythm regulation.[25]

Pathophysiology

Much of the understanding of REM sleep neurocircuitry comes from animal studies, clinical pathologic correlations, and radiographic studies.[11] The anatomical structures that control REM sleep involve mutually inhibiting REM-on and REM-off brainstem nuclei (FIGURE 5-2 [11]). In the REM-on state, glutamatergic neurons in the sublateral dorsal nucleus or subcoeruleus send descending projections to the nucleus raphe magnus along with the ventral alpha gigantocellular and lateral paragigantocellular reticular nuclei of the ventromedial medulla. These second-order neurons send descending γ-aminobutyric acid–mediated (GABA-ergic) and glycinergic inhibitory projections to the spinal motor neurons, which results in motor atonia. In addition, cholinergic and noncholinergic neurons in the sublateral dorsal nucleus,

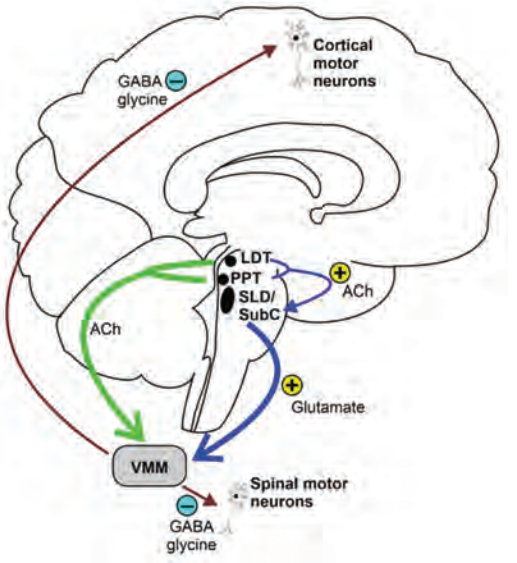

FIGURE 5-2
Neuroanatomical control of rapid eye movement (REM) atonia. The REM-on neurons of the sublateral dorsal nucleus or subcoeruleus (SLD/SubC, *thick blue arrow*), laterodorsal tegmentum (LDT), and pedunculopontine tegmentum (PPT, *thick green* and *thin blue arrows*) activate the ventromedial medulla (VMM) to inhibit motor activity (*thin maroon arrow*).
ACh = acetylcholine; GABA = γ-aminobutyric acid. Reprinted from Figorilli M, et al. Brain Sci.[11] © 2021 by the authors.

laterodorsal tegmentum, and pedunculopontine tegmentum and glutamatergic neurons in the reticular formation send projections to the thalamus and hypothalamus, which may contribute to the cortical activation noted during REM sleep. In the REM-off state, the ventrolateral periaqueductal gray and lateral pontine tegmentum inhibit the sublateral dorsal nucleus and subcoeruleus.[11]

Lesions caused by α-synuclein deposition, stroke, demyelination, and other causes can directly disrupt the sublateral dorsal nucleus, which subsequently can interfere with REM sleep and the mechanisms that preserve REM atonia. The result of this cascade is the clinical manifestation of RBD. Antidepressant medications may induce RBD via disrupted inhibition of REM-on neurons (which control motor atonia in the nondisease state).

Narcolepsy-related RBD may have a separate underlying mechanism. The main pathology in narcolepsy type 1 is the loss of orexinergic neurons in the lateral hypothalamus, which results in sleep/wake instability and disruption of the REM-on/REM-off switch. This instability allows for REM intrusions into wakefulness, with clinical manifestations such as hypnogogic and hypnopompic hallucinations, sleep paralysis, and cataplexy. The sleep-wake instability seen in narcolepsy type 1 also destabilizes REM sleep, which may explain RBD that occurs in people with narcolepsy.

Types of RBD

RBD can be classified into different types based on the associated cause: isolated RBD, secondary RBD, and drug-induced RBD.

ISOLATED RBD. RBD that occurs in the absence of an identified cause is termed *isolated* RBD, previously called *idiopathic* RBD. Since most people with isolated RBD eventually develop a neurodegenerative disease, the term *isolated* is favored over *idiopathic*. Isolated RBD is the type that portends a high long-term risk of neurodegenerative disease, as detailed below (CASE 5-1).

SECONDARY RBD. Secondary RBD refers to RBD in the presence of an associated disorder such as neurodegenerative disease, narcolepsy, focal lesions, and other comorbidities (TABLE 5-2). When a person with isolated RBD develops a neurodegenerative disease, the subtype changes from isolated RBD to secondary RBD.

The most common cause of secondary RBD is neurodegenerative disease, particularly the α-synucleinopathies: dementia with Lewy Bodies, Parkinson disease, and multiple system atrophy. The prevalence of RBD is very high among those with an α-synucleinopathy, with RBD prevalence rates of 30% to 50% in people with Parkinson disease and more than 70% in people with dementia with Lewy bodies or multiple system atrophy.[22]

RBD symptoms can change over the course of the neurodegenerative disease. Dream enactment can remain stable or even decrease, but RWA appears to increase with the progression of Parkinson disease and dementia with Lewy bodies.[26] RBD symptoms can start after Parkinson disease onset, with RBD prevalence increasing from 25% to 52% over the course of Parkinson disease.[26]

In people with known neurodegenerative disease, the presence of RBD predicts worse motor and cognitive function. In those with Parkinson disease, probable RBD is associated with worse motor scores, longer Parkinson disease

KEY POINTS

- RBD is more common in men among people 50 years old or older but can affect men and women equally in those younger than 50 years old.
- Antidepressant medications may induce RBD via disrupted inhibition of REM-on neurons (which control motor atonia in the nondisease state).
- RBD can start after the onset of neurodegenerative disease or can be comorbid with other disorders, such as narcolepsy.
- In people with known neurodegenerative disease, the presence of RBD predicts worse motor and cognitive function.

duration, more cognitive dysfunction, worse olfaction and constipation, and more gait and balance dysfunction.[27,28]

RBD secondary to narcolepsy comprises 10% to 15% of people with secondary RBD overall and 38% in those younger than 50 years old.[29] RBD symptoms are seen in 41.4% of people with narcolepsy type 1 and 13.2% of people with narcolepsy type 2, and RBD is more common in people with narcolepsy type 1 and narcolepsy type 2 who take antidepressants.[30] The events seen in RBD

CASE 5-1

A 59-year-old man presented to the clinic with a 2-year history of moving in his sleep. He had various vivid dreams of being chased by a tiger, attacked by a robber, and having to jump away from an oncoming car. His spouse observed him acting out his dreams three times per week, during which he appeared to be running in the bed, punching, or jumping out of the bed. In the context of this behavior, he had unknowingly hit his spouse twice, both without injuries. The patient once bruised his wrist when he fell out of bed. The events mainly occurred later in the night; his eyes were closed and he could be easily awakened. He sometimes remembered the content of his dreams. He had no other medical history and took no medications. His neurologic examination was normal. In-laboratory polysomnography done with additional forearm EMG leads showed increased muscle activity in the chin, arms, and legs. Some simple movements and occasional punching were seen during rapid eye movement (REM) sleep. His apnea-hypopnea index score was 2 events per hour, and his periodic limb movement index score was 10 events per hour.

The patient was diagnosed with isolated REM sleep behavior disorder (RBD). Safety precautions were discussed, and the patient was advised to pad nearby furniture, place cushions on the floor or install a bed rail, and remove firearms from the bedroom. Clonazepam 0.25 mg nightly was initiated. When asked, the patient indicated that he wanted to know about future health risks associated with isolated RBD. The clinician discussed the risk of neurodegenerative disease over the next several years along with a plan for longitudinal monitoring. After 1 month of clonazepam use, the patient reported only one interval RBD event and no daytime sleepiness. Over 8 years of follow-up, the patient developed a tremor and difficulty fastening buttons. Resting tremor, slight shuffling gait, asymmetric bradykinesia, and rigidity were seen on examination. The patient was diagnosed with Parkinson disease and a dopamine agonist was initiated with improvement in symptoms.

COMMENT

This case highlights a common presentation of isolated RBD, which can be the harbinger symptom prior to the development of a neurodegenerative disease such as Parkinson disease. RBD events typically respond well to clonazepam. In people with RBD and comorbid obstructive sleep apnea, treatment of sleep-disordered breathing is important to determine its contribution to RBD symptoms.

secondary to narcolepsy are more evenly distributed throughout the sleep period compared with the events noted in the setting of isolated RBD, which are more frequent in the second half of the sleep period.[31] The electrophysiologic measurement of the REM atonia index in those with RBD and narcolepsy is lower than in controls but still higher than in those with isolated RBD.[29]

Other neurologic diseases that are uncommon causes of RBD include multiple sclerosis, stroke, tumors, Wilson disease, Huntington disease, autoimmune disorders such as anti-IgLON5, contactin-associated protein-like 2, and leucine-rich glioma-inactivated 1 antibody diseases, and amyotrophic lateral sclerosis.[32,33] Posttraumatic stress disorder (PTSD) is also linked to RBD. RBD occurs in 15% of veterans with PTSD,[34] and RWA is more prominent in people who have PTSD with RBD compared with those who have PTSD without RBD but is less prominent than in isolated RBD. However, in one study the individuals with PTSD-related RBD were all on antidepressants, which may have influenced the amount of RWA observed.[35]

The pathophysiologic links between PTSD and RBD remain unclear. There may be neurochemical and physiologic changes that are not associated with α-synucleinopathies. For example, prolonged stress in animal models can lead to depletion of norepinephrine and neuronal loss in the locus ceruleous.[34] However, it is also possible that this neurotransmitter depletion causes an unmasking of isolated RBD.[36]

RBD in children and young adults is typically secondary to another disorder such as narcolepsy or a neurodevelopmental disorder such as autism.[37] Pediatric RBD can also be due to other symptomatic disorders such as epilepsy, attention deficit hyperactivity disorder, and tumors.[37]

DRUG-INDUCED RBD. Some medications can induce or worsen RBD. The most common agents are antidepressants, particularly SSRIs, SNRIs, and tricyclic antidepressants. One group found that 12.2% of people on antidepressants who underwent polysomnography (excluding those with an α-synucleinopathy, narcolepsy, and progressive supranuclear palsy) had RWA; 48% of that subgroup met diagnostic criteria for RBD.[38] Mirtazapine and monoamine oxidase inhibitors (MAOIs) can also increase REM motor activity,[39] but bupropion does not.[40] Still, most patients on antidepressants do not develop RBD. While the association between antidepressants and RBD raises questions about antidepressants unmasking latent RBD, this relationship is still controversial due to limited data and the fact that depression may be a prodromal symptom of α-synucleinopathies.[21]

Treatment of drug-induced RBD can be challenging. Antidepressant discontinuation or switching to bupropion can help clarify whether the patient has isolated RBD or drug-induced RBD, but it may take several months for symptoms to resolve. Furthermore, antidepressant discontinuation can worsen the underlying mood disorder. Although bupropion can help with depressive symptoms, it does not have a major anxiolytic effect.

Clinicians and patients should discuss the risk-benefit ratio of adjusting antidepressant medications. If antidepressant dose adjustment is considered, the clinician should coordinate care with a psychiatrist, plan the antidepressant taper or cross-titration with bupropion as appropriate, and monitor for worsened mood dysfunction. If the antidepressant cannot be tapered or switched, then symptomatic management should proceed as it would for

KEY POINTS

- **Events seen in RBD secondary to narcolepsy are more evenly distributed throughout the sleep period compared with the events noted in the setting of isolated RBD, which are more frequent in the second half of the sleep period.**
- **The most common causes of drug-induced RBD are antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Symptoms can take several months to resolve after drug discontinuation.**

isolated RBD. If the clinician is unable to confirm the diagnosis of drug-induced RBD via antidepressant discontinuation, they should longitudinally monitor the patient for signs and symptoms of neurodegenerative disease.

Beta-blockers, particularly propranolol, have also been reported to induce RBD symptoms. The mechanism is unclear, but it may involve binding to serotonin receptors or effects on melatonin production.[41] It remains unclear if beta-blocker–associated RBD unmasks latent RBD.

ISOLATED RWA. Cases of isolated RWA without dream enactment symptoms have been reported. Some have termed this prodromal RBD, as a precursor stage to

TABLE 5-2 **Disorders Associated with Rapid Eye Movement Sleep Behavior Disorder**

Neurodegenerative disease

- Parkinson disease[a]
- Dementia with Lewy bodies[a]
- Multiple system atrophy[a]
- Mild cognitive impairment[a]
- Huntington's disease
- Spinocerebellar ataxia types 2 and 3
- Amyotrophic lateral sclerosis
- Pure autonomic failure
- Alzheimer disease
- Progressive supranuclear palsy
- Frontotemporal dementia
- Corticobasal syndrome
- Neurodegeneration with brain iron accumulation
- Prion disease

Autoimmune and paraneoplastic disorders

- Narcolepsy[a]
- Anti-IgLON5 disease
- Anti-LGI1 disease
- Anti-CASPR2 disease
- Anti-NMDA receptor encephalitis
- Anti-Ma1 and anti-Ma2 encephalitis

Metabolic disease

- Wilson disease

CONTINUED ON PAGE 1103

isolated RBD.[42] Since this is a new concept, validated measures for isolated REM sleep without atonia do not exist.[12]

Association With Neurodegenerative Disease

The association between RBD and the development of neurodegenerative disease has been recognized for the past three decades.[3] Phenoconversion refers to the point at which a patient in a prodromal state, such as isolated RBD, is diagnosed with a neurodegenerative disease. It should be noted that neurodegeneration is a continuous process, and those with isolated RBD will often have some evidence of neurodegeneration below the clinical threshold for parkinsonism or cognitive impairment.

CONTINUED FROM PAGE 1102

Psychiatric disorders

- Posttraumatic stress disorder[a]

Developmental disorders

- Chiari malformation
- 22q11.2 deletion syndrome
- Autism spectrum disorder
- Attention deficit hyperactivity disorder
- Smith-Magenis syndrome
- Mobius syndrome

Focal lesions

- Pontine tumors
- Demyelinating plaques from multiple sclerosis
- Pontine ischemia
- Pontine cavernous malformation

Other neurologic disorders

- Essential tremor
- Myotonic dystrophy
- Tourette syndrome
- Autosomal dominant leukodystrophy
- Traumatic brain injury

Medications

- Selective serotonin reuptake inhibitors (SSRIs)[a]
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)[a]
- Tricyclic antidepressants
- Beta-blockers

CASPR2 = contactin-associated proteinlike 2; IgLON5 = immunoglobulinlike cell adhesion molecule 5; LGI1 = leucine-rich glioma inactivated protein 1; NMDA = *N*-methyl-D-aspartate.
[a] Most common causes.

Among neurologic diseases, RBD is particularly linked to synuclein pathology. Among 172 patients who underwent autopsy, 94% had an α-synucleinopathy, including Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. Alzheimer disease was less common and when present was often associated with dementia with Lewy bodies copathology. Progressive supranuclear palsy, an atypical parkinsonian disorder associated with tau protein inclusions, was seen in only 2 out of 172 cases (CASE 5-2).[43]

CASE 5-2

A 75-year-old woman presented with episodes of screaming and falling out of bed during sleep. The patient had been diagnosed 2 years prior with dementia with Lewy bodies. While awake, she occasionally had visual hallucinations of people, but these hallucinations were not frightening or bothersome. She needed help with daily activities including cooking, cleaning, and finances. Over the past 1 year, she screamed in the night twice per week. Her caregiver had observed her sometimes punching the bed or in the air. She once fell out of bed in her sleep and bruised her hip. The movements occurred in the last half of the sleep period. Her caregiver could wake her easily during events. She did not remember any dreams. She could get confused at night and sometimes needed to be reoriented. She did not get up and walk around the house except for using the bathroom for nocturia once nightly. She occasionally snored. She took amlodipine for hypertension and donepezil for dementia.

On examination, she had a body mass index of 24 kg/m^2, abnormal clock drawing, and mild parkinsonism. The option of a diagnostic in-laboratory polysomnogram was discussed, but the caregiver worried that the patient may get more confused and agitated in the sleep laboratory. Due to this concern, a home sleep apnea test was done and showed an apnea-hypopnea index score of 3 events per hour and no evidence of obstructive sleep apnea. A diagnosis of probable rapid eye movement sleep behavior disorder (RBD) was made. Melatonin 3 mg nightly was recommended and titrated to 6 mg for persistent events. On follow-up 1 month later, the caregiver reported a 75% improvement in RBD events and screaming. The patient had no medication side effects, with no worsening of daytime sleepiness and balance.

COMMENT

Diagnosis and management of RBD can be challenging in people with dementia. While in-laboratory polysomnography is necessary for the diagnosis of RBD, patients with dementia may not tolerate the study in an unfamiliar environment with a myriad of electrodes. In the context of dementia with Lewy bodies, the patient's presenting symptoms were consistent with RBD; however, given the history of snoring and hypertension, it was important to evaluate for obstructive sleep apnea as it can mimic or worsen RBD. Although clonazepam can be effective for RBD, this medication may worsen cognitive function and balance in people with dementia with Lewy bodies.

The phenoconversion rate among studies slightly varies by cohort. The median time to phenoconversion is about 8 years after RBD diagnosis,[21] with a phenoconversion rate of 33% by 5 years follow-up and 60% to 73% by 10 years.[21,44] The longer the duration of follow-up, the higher the total phenoconversion rate, as high as 96% by 14 years.[44] One cohort study reported an annual phenoconversion rate of 8.3%, although this rate may not be linear.[6] People with isolated RBD may have evidence of neurodegeneration, including decreased dopamine transporter tracer binding on single-photon emission computed tomography (SPECT) imaging[45] and substantia nigra hyperechogenicity on transcranial sonography (particularly when mild motor symptoms are present).[46]

Since the recognition that RBD is an α-synucleinopathy prodrome, many biomarkers have been identified to predict phenoconversion. Clinical biomarkers include male sex, frequency and duration of active dream enactment behaviors, cognitive dysfunction, hyposmia, constipation, depression, hypersomnia, motor dysfunction, age, erectile dysfunction, color vision abnormalities, and orthostatic hypotension.[6,21]

Imaging biomarkers include reduced dopamine transporter binding[6,21] and substantia nigra hyperechogenicity.[46] Higher free water on diffusion tensor imaging was seen in isolated RBD but it is unclear if this finding predicts phenoconversion.[47]

Electrophysiologic markers include shorter sleep duration, higher frequency of periodic limb movements in sleep associated with arousals, diffuse electroencephalographic slowing during wakefulness, and higher delta power and lower alpha power in central and occipital regions in REM sleep.[48] Mixed data exist on whether RWA predicts phenoconversion.[9,21]

Pathologic markers include α-synuclein deposits in the enteric nervous system, salivary glands, and skin. Nasal mucosa α-synuclein has low sensitivity but is very specific and may be more helpful in those with olfactory dysfunction to determine if the hyposmia is prodromal or due to another cause such as smoking or head trauma. The presence of α-synuclein in the CSF can be detected in 85% to 90% of isolated RBD cases but only in up to 10% of controls.[49,50]

Attempts have been made to determine which combination of these many potential risk predictors best predicts phenoconversion.[51] The strongest individual risk factors are video polysomnography–confirmed RBD, dopamine transporter imaging abnormality, and orthostatic hypotension. The strongest predictive combination of a limited set of risk factors is dopamine transporter imaging abnormality, constipation, and age older than 70 years,[52] although another study suggested that abnormal dopamine transporter imaging, olfactory loss, orthostatic hypotension, and motor dysfunction are the strongest predictors.[53]

KEY POINTS

- People with isolated RBD have a high lifetime risk of neurodegenerative disease, particularly α-synucleinopathies; about one-half of those with RBD will develop a neurodegenerative disease over 8 years of follow-up after RBD diagnosis.
- Factors that predict an increased risk of phenoconversion in isolated RBD include abnormal dopamine transporter and substantia nigra imaging, pathologic markers, and autonomic, motor, and cognitive dysfunction.

Management

Management of RBD includes patient education, suppressing dream enactment events and implementing safety precautions to reduce the risk of injury, treating nightmares, and, in the case of isolated RBD, counseling on the risk of neurodegeneration.[54] Violent dreams associated with RBD can cause distress and concern for the patient and family. Education about the lack of correlation between dream enactment behaviors and the patient's personality and the typical characteristics of RBD can provide insight and reassurance for the patient and family.

Safety precautions should always be reviewed to lower injury risk to the patient and their bed partner.[54] Each of these environmental adjustments may lower the risk of injury to the patient: pad or remove nearby furniture; remove nearby sharp objects, weapons, or other potentially injurious objects; add a bedrail; or lower the mattress. Bed partners often sleep in another bed by the time of clinical presentation; for those in the same bed, sleeping apart or the addition of a barrier may be recommended. In people with refractory RBD, a pressurized bed alarm can be used to wake patients if significant movement occurs.[55]

If the patient takes an antidepressant that can worsen RBD symptoms, a risk-benefit consideration is needed to decide whether to taper or switch the medication, with the knowledge that the symptoms may take weeks to months to improve. Coexisting sleep apnea should also be treated as this can mimic or worsen RBD symptoms.[16] If RBD symptoms dramatically improve with sleep apnea management, repeat polysomnography on treatment can be considered to see if the RWA also improved, although the long-term clinical implications of this finding are uncertain.

Pharmacotherapy should be based on the frequency and intensity of RBD events, prior injuries sustained due to the behavior, the presence of nightmares, and patient preference. Several medications have been studied, with the most data available on clonazepam and melatonin.[54] The choice of medication will also depend on the subtype of RBD and the patient's comorbidities (eg, dementia, sleep apnea). Several limitations influence the selection of optimal medication therapy or the benefits of monotherapy versus combination therapy. Many studies were retrospective or open-label trials, although randomized clinical trials exist for some medications. The outcome measures for RBD improvement have also varied significantly across studies, which limits comparability.[32] Most studies used questionnaires or self-reporting; since patients are not always aware of the events, such measures are not fully reliable. Polysomnography is an objective measure but is costly and one night of observation may not reflect the full extent of the behaviors. More objective measures are needed, particularly in the home setting, to help guide treatment decisions.

Clonazepam was one of the first medications used to treat RBD. Its use stemmed from its ability to control other types of movements during sleep and waking states. Several observational studies demonstrated its ability to suppress dream enactment behavior in isolated RBD and secondary RBD.[5,56] While its mechanism in improving RBD is unclear, it may work through enhanced GABA-ergic and glycinergic inhibition of spinal motor neurons.[57] Clonazepam may improve some phasic movements but does not appear to improve overall RWA, simple motor movements, or vocalizations, suggesting other mechanisms may be involved in major motor event suppression, such as through altering dream content.[58,59]

Clonazepam is dosed 0.25 mg to 4 mg 30 to 60 minutes before bedtime. Interestingly, tolerance does not appear to occur with long-term use of clonazepam for RBD.[60] The main side effects include daytime somnolence, confusion, and gait imbalance, which may be of particular concern in those with neurodegenerative disease.

Melatonin, a hormone involved in circadian regulation, is secreted at night in dim light conditions. Its mechanism in RBD has been elusive, although one hypothesis includes restoration of the circadian system.[61] Several retrospective studies and a few clinical trials studied immediate-release melatonin along with a few studies on sustained-release melatonin. Most

studies have shown improvement in dream enactment behavior frequency and intensity with immediate-release melatonin[32]; however, a recent trial using sustained-release melatonin did not show improvement in dream enactment behavior.[62] The data on melatonin's effect on RWA have not been consistent.

Melatonin is typically dosed between 3 mg and 12 mg nightly, with most patients responding to 6 mg to 9 mg nightly. Potential side effects include headaches and nightmares, and some patients report daytime sleepiness. In the United States, melatonin is a nutraceutical and is available over the counter. The lack of standardization in manufacturing and the variety of melatonin preparations (eg, tablet, capsule, chewable, gummy) can be a challenge and source of confusion for patients.

Cholinesterase inhibitors, such as rivastigmine and donepezil, are often used for cognitive symptoms in people with dementia with Lewy bodies or Parkinson disease. Two randomized crossover trials using rivastigmine 4.6 mg daily showed improvement in RBD symptoms in those with comorbid Parkinson disease[63] or mild cognitive impairment.[64] Much less data are available for donepezil, and those that currently exist show mixed results.[65] The potential mechanism may involve increased cholinergic transmission, which may potentiate REM atonia.

Several other treatments have been examined for RBD symptoms. Observational studies on pramipexole have reported improvements in dream enactment behaviors in people with isolated RBD.[32] Sodium oxybate also appears beneficial for RBD symptoms and may improve REM atonia in adults and children with narcolepsy.[66,67] A recent clinical trial of sodium oxybate in treatment-resistant RBD (isolated and associated with Parkinson disease) showed improvements in RBD event frequency within the treatment group; however, possibly due to a strong placebo effect, no differences were seen between the sodium oxybate and placebo groups.[68] Recently, safinamide over 3 months in a crossover study improved RBD in Parkinson disease patients.[69]

To date, no medications have been proven to modify the disease course in people with neurodegenerative α-synucleinopathies. Important factors in these negative results may be a lack of biomarkers sensitive to change and testing too late in the disease course. Such trials in patients with isolated RBD are difficult given the long latency to phenoconversion. A study aimed at reducing the risk of phenoconversion by 50% over 2 years of therapy would require 142 to 366 patients per arm.[21] While enrollment of people at higher risk of phenoconversion can reduce the study duration, the findings may not be generalizable to those without such risk factors, and the extent of neurodegeneration may still be too great to alter the course of and response to treatment. Therefore, it is vital to identify and validate neurodegeneration biomarkers that are sensitive to changes in isolated RBD. To better understand the disease, determine such biomarkers, and prepare for these trials, it is important to inform people with isolated RBD as appropriate about the risk of neurodegeneration and opportunities to participate in clinical research if they so choose. In the meantime, exercise should be recommended for patients with isolated RBD given that some evidence shows that exercise confers neuroprotection and is beneficial for general health.[32]

Risk Disclosure

Disclosure of the risk of neurodegeneration to people with isolated RBD is a potential source of controversy. The reasons for the controversy are a

KEY POINTS

- **Reviewing safety precautions with patients (eg, pad or remove nearby furniture, remove potentially injurious objects, add a bedrail to reduce risk of injury) is critical to reducing the risk of injury from dream enactment behavior.**
- **Clonazepam and melatonin are the first-line agents to suppress dream enactment behaviors. Treatment choice requires consideration of the RBD subtype and comorbidities, such as dementia.**

lack of consensus on disclosure methodology, the variable and often long latency to phenoconversion, a lack of disease-modifying therapies, and that RBD symptoms may not be the patient's presenting complaint.[70]

Several ethical principles need to be balanced when considering risk disclosure: beneficence, nonmaleficence, and autonomy. Beneficence requires that clinicians act in the best interest of the patient, to allow the patient to prepare for the future and consider potential risk-reduction strategies. Nonmaleficence requires that clinicians "do no harm"; disclosure about the high risk of neurodegenerative disease, even if years away, can lead to anxiety. When a disease-modifying strategy is available, beneficence and nonmaleficence are aligned; however, in the case of isolated RBD, they may not be. The principle of autonomy affirms that patients have a right to know about their health and prepare for the future. It also asserts that patients have a right to not know, as some patients may not want to be concerned with a potential disease that may never develop.

Two general approaches exist for disclosure about the risk of phenoconversion to neurodegenerative disease: full disclosure and watchful waiting. The benefits of full disclosure include respect for the patient's right to know, inclusion of patients in decision making about their health, facilitation of early neurodegenerative disease monitoring, and ability of patients and families to discuss future care planning, life goals, and finances, and participate in clinical research. The risks of full disclosure include potential anxiety and hopelessness when there is long phenoconversion latency and no available disease-modifying therapy. However, information about the association between isolated RBD and neurodegeneration is available on the internet; if the clinician withholds disclosure and the patient reads about this association on their own, trust in the patient-clinician relationship may be damaged.[71] Watchful waiting entails monitoring without risk discussion but allowing for such discussion if the patient later wishes.

A patient-centered approach to risk disclosure has been published. Patients should be provided with the option to learn about the risk of phenoconversion to neurodegenerative disease. If the patient does not wish to be informed, the clinician can offer to discuss it at another time. If the patient does want to be informed, the patient should indicate the extent of

TABLE 5-3 ***ICSD-3-TR* Diagnostic Criteria for Recurrent Isolated Sleep Paralysis[a]**

***International Classification of Sleep Disorders, Third Edition, Text Revision* criteria A through D must be met for a recurrent isolated sleep paralysis diagnosis:**

- **A** A recurrent inability to move the trunk and all of the limbs at sleep onset or upon awakening from sleep
- **B** Each episode lasts seconds to a few minutes
- **C** The episodes cause clinically significant distress, including bedtime anxiety or fear of sleep
- **D** The disturbance is not better explained by another sleep disorder (especially narcolepsy), medical disorder, mental disorder, or medication or substance use

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information desired. When possible, individualized risk stratification should be pursued.[70]

RECURRENT ISOLATED SLEEP PARALYSIS

Sleep paralysis is a phenomenon that can occur in healthy people or in association with disorders and has garnered much cultural curiosity.

Clinical Historical Features and Diagnosis

Sleep paralysis is a phenomenon of waking from sleep unable to move the trunk or limbs for seconds to a few minutes until it resolves spontaneously or in response to an external stimulus. The diaphragm is spared but accessory respiratory muscles are not, which can lead to a sensation of a weight on one's chest. Sleep paralysis can be associated with visual, auditory, or tactile hallucinations or a feeling of a presence in the room.[72] Sleep paralysis has taken on various cultural meanings and has been expressed in several works of art such as Henry Fuseli's *The Nightmare* in 1781.

Sleep paralysis occurs in the transition between REM sleep and waking. Polysomnographic studies show an intrusion of EEG alpha activity into REM sleep, followed by an arousal and persistence of REM atonia into wakefulness. Those with sleep paralysis have no difference in REM macrostructure or fragmentation but do have higher bifrontal EEG beta activity in REM sleep.[73] Episodes may even occur during a sleep-onset REM period.

Sleep paralysis occurs in at least 7.6% of the population,[72] and 15% to 40% of people younger than 30 years old experience it at least once.[4] Sleep paralysis itself is benign and is not a common reason for people to seek medical care. When sleep paralysis is recurrent, the most common cause is narcolepsy. However, it may occur in an isolated form and cause clinical distress, a disorder known as recurrent isolated sleep paralysis.

Causes and Associations

Sleep paralysis can be triggered by sleep deprivation, jet lag, shift work, and supine sleep, and is more common in those with PTSD.[74,75]

The diagnosis of recurrent isolated sleep paralysis is established by the patient's history (TABLE 5-3[4]), and there is no specific frequency threshold.[4] Still, polysomnography should be considered if the clinician suspects another condition such as sleep apnea, narcolepsy, or sleep-related seizure. The differential diagnosis also includes sleep terrors, nightmare disorder, lucid dreaming, RBD, and hypokalemic periodic paralysis.

Management

Sleep paralysis is self-limiting and does not typically impact daytime function, so patient education and reassurance are the mainstays of recurrent isolated sleep paralysis management. Identifying triggers, maintaining good sleep hygiene and a consistent sleep schedule, and routinely sleeping at least 7 hours each night can help mitigate recurrent isolated sleep paralysis. Because events are more likely to occur when supine, positional therapy to prevent supine sleep may be helpful. The bed partner, if present, should be instructed to touch the patient if they hear soft vocalizations in the morning hours before full awakening.[74] Medications are rarely needed. Available data on pharmacologic therapy for sleep paralysis are based on studies of people with narcolepsy. Tricyclic or other

KEY POINTS

- Patients should be offered information on the potential health risks of RBD, and if desired more specific information on the risk of neurodegeneration should be provided.
- Recurrent isolated sleep paralysis involves repeated episodes of sleep paralysis that cause distress and are not associated with another underlying disorder such as narcolepsy.
- Sleep paralysis can be triggered by sleep deprivation, jet lag, shift work, and supine sleep, and is more common in those with posttraumatic stress disorder.

antidepressants for sleep paralysis and cognitive behavioral therapy for insomnia for coping strategies may be helpful.[74]

NIGHTMARES AND NIGHTMARE DISORDER

While nightmares are common and occur sporadically in healthy people, they can also become recurrent and distressing as part of a disorder, such as nightmare disorder or PTSD. Nightmares can significantly impact sleep and quality of life and can respond to pharmacologic and cognitive behavioral therapies.

Clinical Features and Diagnosis

Nightmares are disturbing, frightening dreams that usually involve threats to self or others. Sporadic nightmares are common and do not typically present clinically. With nightmare disorder, one experiences recurrent and extended nightmares that cause distress or functional impairment (TABLE 5-4).[4] While no frequency criterion is required for diagnosis, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* specifies severity based on nightmare frequency (mild: less than one episode per week; moderate: at least one episode per week but less than nightly; severe: episodes nightly).[76]

Nightmares are strongly linked to psychiatric disorders. Symptoms of anxiety and depression are both commonly associated with nightmares, which can worsen mood disruption.[77] Nightmares are seen in 66.7% of people with PTSD and are common among combat veterans.[74,78] In fact, persistent reexperience of the traumatic event is part of the diagnostic criteria of PTSD.[76] Nightmare disorder can also be idiopathic.

TABLE 5-4 *ICSD-3-TR* Diagnostic Criteria for Nightmare Disorder[a]

***International Classification of Sleep Disorders, Third Edition, Text Revision* criteria A through C must be met for a nightmare disorder diagnosis:**

- **A** **Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity**
- **B** **On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert**
- **C** **The dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following:**
  - **1** Mood disturbance (eg, persistence of nightmare affect, anxiety, dysphoria)
  - **2** Sleep resistance (eg, bedtime anxiety, fear of sleep/subsequent nightmares)
  - **3** Negative impact on caregiver or family functioning (eg, nighttime disruption)
  - **4** Behavioral problems (eg, bedtime avoidance, fear of the dark)
  - **5** Daytime sleepiness
  - **6** Fatigue or low energy
  - **7** Impaired occupational or educational function
  - **8** Impaired interpersonal or social function

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The evaluation of nightmares requires a detailed sleep history, with characterization of the dreams and their frequency. PTSD-related nightmares are more aligned with the trauma and involve more arousals and feelings of helplessness.[79] Other elements to query include psychiatric and trauma history, suicidal ideation and attempts, medication use, and substance use.[80] RBD symptoms are also common in those with PTSD.[34] Risk factors for nightmares include migraine, bronchitis, asthma, beta-blocker or SSRI use, and alcohol withdrawal.[74] Polysomnography can be helpful if comorbid sleep apnea, RBD, or narcolepsy is suspected.

Nightmares occur sporadically in 22% of adults and frequently in 3% to 4% of adults.[74] In those with psychiatric disease, nightmare prevalence ranges from 37% in those with mood disorders to 67% in those with PTSD. Nightmares are more common in women and are associated with higher rates of insomnia, daytime sleepiness, fatigue, impaired concentration, anxiety, depression, and poor academic performance. While general prevalence studies did not separate nightmares from nightmare disorder, the latter is thought to occur in 2% to 6% of adults.[77] In children, the prevalence of nightmares at least once weekly is 19%.[80]

The pathogenesis of nightmares is thought to involve elevated hyperarousal and impaired fear extinction.[79] Nightmares may act as a conditioning stimulus, which results in sleep avoidance behaviors. Polysomnographic findings in young adults with nightmares include more awakenings, an increase in the EEG alpha rhythm spectral power, and more non-REM to REM transitions.[74]

Management

Prazosin 1 mg to 15 mg nightly is the first-line pharmacologic treatment for nightmare disorder and PTSD-associated nightmares. Prazosin, an α_1-adrenergic receptor antagonist, has been repeatedly shown to benefit people with PTSD who experience nightmares. The medicine was previously recommended by published guidelines,[81] but a recent large multicenter study failed to show improvement in PTSD-related nightmares, which resulted in a downgraded recommendation.[82] However, a recent meta-analysis that included the negative trial still supports the use of prazosin.[83] Orthostatic hypotension is a prominent side effect of prazosin.

Other medications studied for the treatment of nightmare disorder include nabilone (a synthetic cannabinoid), topiramate, and gabapentin. Clonazepam and venlafaxine do not appear to improve nightmares, and there are recommendations against their use in the treatment of nightmare disorder.[82]

Several types of nonpharmacologic therapies can be used for the treatment of nightmare disorder. Cognitive behavioral therapy generally addresses the negative thoughts, emotions, and maladaptive behaviors that may occur in conjunction with nightmare disorder. Image rehearsal therapy is specifically recommended for the treatment of nightmare disorder.[82] Image rehearsal therapy attempts to alter the content of nightmares by exposure to the nightmare content and rehearsal during the day to replace the nightmare with a positive script. The intentional change and its rehearsal appears to decrease the activation of fear circuitry. Several trials have shown the efficacy of image rehearsal therapy in people with PTSD and non-PTSD nightmares, and the benefits can be sustained for years. Image rehearsal therapy can be combined with other cognitive behavioral therapy strategies and can be provided with limited face-to-face contact or with online programs.[79] Exposure, relaxation, and rescripting

KEY POINTS

- Management of recurrent isolated sleep paralysis may include reassurance, behavioral strategies, positional therapy, and tricyclic or other antidepressants.
- Nightmares are distressing, frightening dreams that involve threats to self or others. In nightmare disorder, one has recurrent nightmares that result in distress or functional impairment.
- Nightmares are common in people with posttraumatic stress disorder and tend to be related to the traumatic incident.
- Management of nightmare disorder includes cognitive behavioral therapy, particularly image rehearsal therapy, and medications such as prazosin.

therapy, a type of image rehearsal therapy delivered over 3 weeks, provides additional sleep hygiene education, progressive muscle relaxation, and trauma exposure with rescripting of the nightmares.[82] Other nonpharmacologic options include lucid dreaming, sleep dynamic therapy, and systematic desensitization.

CONCLUSION

RBD is a REM sleep parasomnia in which people may have vivid dreams or nightmares and manifest dream enactment behaviors that can disrupt sleep and cause injuries to people and their bed partners. Polysomnography remains necessary for diagnosis to confirm the presence of RWA and exclude RBD mimics. The implementation of safety precautions to reduce injury and judicious medication use to suppress dream enactment behavior are important management strategies. While RBD is often seen in those with neurodegenerative diseases, particularly α-synucleinopathies, it can also occur as a prodromal marker seen many years prior to neurodegenerative disease onset. As prodromal biomarkers become better understood, future disease-modifying agents may reduce the risk of, or even prevent, the development of neurodegenerative disease. Recurrent isolated sleep paralysis is an uncommon parasomnia that is self-limited but can be controlled if symptoms cause distress. Finally, nightmare disorder can be idiopathic but is often seen in people with PTSD. Nightmare disorder treatment is best managed with image rehearsal therapy but medications such as prazosin can be beneficial.

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VIDEO LEGEND

VIDEO 5-1 REM SLEEP BEHAVIOR DISORDER
A 60-year-old man with isolated rapid eye movement (REM) sleep behavior disorder showing arm and body movements and vocalizations during REM sleep.

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Non–REM Sleep Parasomnias

By Andrew R. Spector, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **Non–rapid eye movement (non-REM) parasomnias are common across the lifespan. This article describes the manifestations, diagnosis, and management of non-REM parasomnias in adults and discusses the social implications of these conditions.**

LATEST DEVELOPMENTS: **Non-REM parasomnias represent a hybrid state of wakefulness and sleep, often triggered by events that increase the frequency of arousals or make it more difficult to fully arouse from sleep. Sleep deprivation, certain medications, and untreated obstructive sleep apnea are known to provoke parasomnias, particularly in those who are genetically predisposed. Non-REM parasomnias include disorders of arousal (ie, sleepwalking, sleep terrors, and confusional arousals), sleep-related eating disorder, and exploding head syndrome. Clinical overlap exists between sleep-related eating disorder and disorders of arousal, suggesting that sleep-related eating disorder may be a fourth disorder of arousal or a manifestation of sleepwalking. Exploding head syndrome is a unique parasomnia of uncertain etiology.**

ESSENTIAL POINTS: **Non-REM parasomnias can range from minor nuisances to severe, life-altering events. While some patients with non-REM parasomnia experience significant consequences during sleep, wakefulness, or both, non-REM parasomnias do not pose a major risk to most patients. For all patients with non-REM parasomnias, safety should be explicitly discussed and addressed. Nonpharmacologic treatment should be prioritized, as increasing total sleep time, avoiding triggering substances, and treating comorbid sleep disorders is often sufficient for the management of non-REM parasomnias. If symptoms persist despite these interventions, treatment with clonazepam or other medications can be considered.**

INTRODUCTION

Parasomnias are unusual and typically unwanted events that occur during and immediately around sleep. These events can be verbal, behavioral, sensorial, emotional, or any combination thereof. Parasomnias are divided into those associated with non–rapid eye movement (non-REM) sleep and those associated with REM sleep. This review will encompass non-REM parasomnias in adults, including the three disorders of arousal—sleepwalking (somnambulism), confusional arousals, and

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RELATIONSHIP DISCLOSURE:
Dr Spector has received personal compensation in the range of $500 to $4999 for serving as an expert witness for Shevlin Smith, and in the range of $10,000 to $49,999 for serving as an editor, associate editor, or editorial advisory board member for *Neurology Today*. The institution of Dr Spector has received research support from Harmony Biosciences. The institution of an immediate family member of Dr Spector has received research support from the American Academy of Allergy, Asthma, and Immunology Foundation, the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases, and the Thurston Arthritis Research Center at the University of North Carolina at Chapel Hill.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Spector discusses multiple medications and therapies for the treatment of non-rapid eye movement parasomnias, none of which are approved by the US Food and Drug Administration (FDA).

sleep terrors—along with sleep-related eating disorder and exploding head syndrome.

While the *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*) groups sleepwalking, confusional arousals, and sleep terrors under the broader heading of Disorders of Arousal and considers sleep-related eating disorder a separate entity,[1] this taxonomy is a matter of ongoing debate. Together, these fascinating conditions represent a mixed state of consciousness with elements of both sleep and wakefulness.[2] This article reviews the clinical presentations, describes what is known about the underlying pathophysiology, and discusses the treatment options and social implications of non-REM parasomnias. For a discussion of non-REM parasomnias in the

CASE 6-1

An 18-year-old college freshman presented to a sleep disorder clinic after his roommate complained about his sleep-related behavior. He had no memory of the event and presented the history as told to him by his roommate. About 2 hours after falling asleep, the patient got out of bed and started moving the sofa across the room. The commotion awakened the roommate, who asked the patient why he was moving the sofa but got no response. The roommate observed the patient move the coffee table, then walk back to bed and go to sleep. In the morning, the patient was surprised to see the furniture had been moved and asked his roommate how it happened. The night of his episode he was up particularly late and had two beers. He notes no other unusual circumstances, new medications, or medical problems.

The patient related a history of sleepwalking starting around age 8 years. Events were infrequent, about two to three times per year, and not associated with injury. He remembered seeing a pediatrician for this as a child and being told that he would outgrow the behavior. The events seemed to resolve as he aged, and he was not aware of any taking place during high school. He was very worried about what else he might do in his sleep.

COMMENT

This case of sleepwalking demonstrates the significance of insufficient sleep and potential triggers, such as alcohol, in bringing out a latent parasomnia. While sleepwalking is common in children, many will outgrow it. The environment of college, however, can be full of parasomnia triggers. Given that this was an isolated, provoked episode of sleepwalking, it would be premature to initiate pharmacotherapy. The patient should be given parasomnia education, reassurance, and counseling about the importance of obtaining a sufficient duration of sleep. He should also be encouraged to review sleepwalking safety with his roommate to ensure there are no dangerous obstacles on the floor or weapons nearby. The roommate can be advised to steer him back into the room if he hears the door open at night. If additional episodes occur, safety counseling should include guidance to keep car keys and kitchen knives inaccessible during sleep and to consider placing an alarm on the bedroom door.

pediatric population, refer to the article "Sleep Disorders in Childhood," by Althea Robinson Shelton, MD,[3] in this issue of *Continuum*.

CLINICAL PRESENTATION

While sometimes difficult to obtain from the patient alone, a thorough history, preferably including a bed partner or observer, can help distinguish between the various types of parasomnias.

Disorders of Arousal

The three disorders of arousal share many characteristics and diagnostic criteria. They can co-occur in the same individual and likely represent different manifestations of similar underlying pathologies; thus, it can be helpful to consider them on a spectrum rather than as three distinct disorders. Disorders of arousal involve recurrent episodes of incomplete awakening, typically from stage N3 sleep (also known as *deep sleep* or *slow-wave sleep*), in which the patient demonstrates reduced or absent responsiveness to external stimuli while displaying wakelike behavior. Although dreamlike mentation has been reported with non-REM parasomnias, these events are not classically associated with dream imagery, which helps distinguish them from REM sleep behavior disorder.[4] Affected individuals tend to have limited or absent memory for behavior that occurs during a non-REM parasomnia.

SLEEPWALKING. The most well-known disorder of arousal is sleepwalking (CASE 6-1). Sleepwalking has been part of the human experience and collective consciousness for millennia, with depictions in medical history (eg, Hippocrates' *On the Sacred Disease* includes a depiction thought to represent sleepwalking) and literature (eg, Shakespeare's *Macbeth*). The feature that distinguishes sleepwalking from the other disorders of arousal is that sleepwalking requires the individual to leave the bed. Ambulation is the typical manifestation and the symptom for which the condition is named, but patients can also perform relatively complex tasks while sleepwalking. Reports of complex sleepwalking behavior include rearranging furniture, consuming food or drink, urinating in inappropriate places, and violence (CASE 6-1).[5-7] When food consumption becomes the predominant behavioral manifestation of sleepwalking, the clinical entity is referred to as sleep-related eating disorder, which is most likely a variant of sleepwalking but is listed independently in the *ICSD-3-TR*.[1] Sleepwalking can continue for over half an hour, although many episodes are shorter than this.[6] Patients who sleepwalk will tend to return to bed and fall back asleep if left alone, but they can also frequently be steered back to bed by observers. The lifetime prevalence of sleepwalking is 22.4%, but the prevalence of sleepwalking in the adult population is low, around 1% to 4%, with a possible slight male predominance.[7-11] Serious injuries resulting from sleepwalking are rare, but the precise frequency is unknown.

SLEEP TERRORS. Sleep terrors, sometimes referred to as night terrors, are highly disturbing events characterized by episodes of intense fear with abrupt onset arising from non-REM sleep (CASE 6-2). These events often begin with a loud scream and are accompanied by the autonomic manifestations of fear: mydriasis, tachycardia, tachypnea, and diaphoresis.[1] As with all disorders of arousal, a sleep terror occurs in the setting of altered consciousness, and amnesia for the event is

KEY POINTS

- Sleepwalking, sleep terrors, and confusional arousals are collectively known as disorders of arousal.
- Disorders of arousal are characterized by a mixed state of sleep and wakefulness with reduced awareness, responsiveness, and recall despite performing behaviors that would typically only occur when awake.
- People who sleepwalk can perform surprisingly complex tasks, often in a manner and with results that would not be expected if they had been fully awake.
- Sleep terrors are distinct from nightmares. Sleep terrors occur earlier in the night and are followed by limited recall, whereas nightmares tend to be later in the sleep period with good post-event recall.

common although not required for diagnosis. Adults with sleep terrors are sometimes able to describe the fears to which they are reacting. These fears usually do not persist during wakefulness, and patients are not typically fearful of the stimulus to which they were reacting while asleep. However, in the moment, they might have the sense that an intruder or a giant spider is attacking them.[12] Patients with sleep terrors may ambulate during an episode, often in an attempt to flee from the source of their terror, such as to lock themselves in a bathroom. The episode may terminate when an observer turns on the lights, although this does not work in all cases. Otherwise, the event will resolve after several minutes to as long as 20 minutes or more.[6] Sleep terrors affect less than 1% of the adult population.[8,11]

Sleep terrors are not typically associated with dream recall; this feature is clinically different from nightmares, which are considered a phenomenon of REM sleep and are usually associated with very good recall and no overt

CASE 6-2

A 49-year-old surgeon presented to a sleep disorder clinic for help controlling screaming episodes at night. She reported that her events started during her surgery residency when she was particularly sleep deprived. The events began consistently 30 minutes after falling asleep and would last for about 1 minute. She reported sitting up in bed and screaming. She experienced severe anxiety during the events, and she retained partial memory when they were over. Her anxiety during the events was focused on having forgotten to do something important. She could quickly fall back asleep after the event concluded. It never reoccurred during the night. She had never become violent or gotten out of bed during an episode. The events were most disturbing to her teenage children who were very frightened by their mother screaming at night. The events occurred about three nights out of the week. She had no history of sleep terrors, sleepwalking, or any other parasomnia as a child; however, her mother had a history of sleepwalking as a child and as an adult. The patient had a history of sleep initiation insomnia and was given triazolam 0.125 mg for her insomnia and parasomnia. She found that the triazolam reduced her sleep latency but did not reduce her screaming events. She requested an alternative to a benzodiazepine as she did not want to take one chronically. She then started melatonin 3 mg nightly, made a concerted effort to avoid sleep deprivation, and experienced a reduced frequency of events.

COMMENT

This case illustrates an adult with sleep terrors. Adults, more often than children, will be only partially amnestic for the fearful stimulus that induces the screaming; this patient had the sense of forgetting something important. This case also highlights the common finding of a family history in people with non-REM parasomnias and the critical role of obtaining adequate sleep duration to prevent non-REM parasomnia occurrence. For this individual, increased total sleep time helped to reduce the frequency of events.

associated behaviors. If the sleep terror is associated with jumping out of bed, REM sleep behavior disorder should be considered within the differential diagnosis. In these situations, the presence of good recall for the dream content would point more toward REM sleep behavior disorder and less toward a sleep terror. Depending on the clinical scenario, polysomnography may be necessary to identify the type of parasomnia.

CONFUSIONAL AROUSALS. Confusional arousals are altered states of consciousness arising from non-REM sleep that lack ambulation and are not associated with terror. Instead, they manifest as confusion experienced while still in bed with the patient sitting up and looking around with confusion until the episode passes. A distinct form of confusional arousal is sleep-related sexual behavior, commonly referred to as *sexsomnia*.[13] Sexual behavior during sleep can range from masturbation to assault, with substantial legal and relationship ramifications (CASE 6-3).

Confusional arousals might be the most common of the disorders of arousal with an adult prevalence of up to approximately 4%.[9] An association with shift

CASE 6-3

A 33-year-old woman presented to a sleep disorder clinic for an evaluation of sexsomnia. She reported that several times per month her boyfriend would wake up and observe her masturbating. She reported that he considered this to be an insult to his masculinity and threatened to leave her if this behavior continued. She reported no memory of doing this but did not doubt him. His threats caused her great distress, and she sought help in getting these episodes to stop. Additional history revealed sleep deprivation resulting in only 5 to 6 hours of sleep per night. She had no risk factors for obstructive sleep apnea, no other past medical history, and no history of trauma or abuse. She had no personal history of sleepwalking, nor did she know of similar episodes among family members. She was counseled about the role of sleep deprivation in promoting parasomnias and was encouraged to get 7 to 8 hours of sleep per night. She was also given a prescription for clonazepam 0.5 mg nightly to use while she worked on improving her total sleep time. Personal safety with concern for intimate partner violence was also discussed. No polysomnogram was ordered as it was felt that it would likely be low yield. At her follow-up visit 3 months later, she reported both improved total sleep time and resolution of episodes, and she was no longer taking the clonazepam.

COMMENT

This is a classic example of sexsomnia in that the patient displayed sexual behavior while asleep with amnesia for the event. This case illustrates the importance of sleep deprivation in the development of parasomnias. This patient had no known personal or family history of any disorder of arousal but displayed sexual behaviors in sleep after years of chronic, inadequate sleep. Although clonazepam was prescribed, her most effective therapy was to increase her total sleep time.

work, other sleep disorders, and psychiatric diagnoses, especially bipolar disorder, has been reported.[14]

OTHER PARASOMNIAS

Two additional parasomnias, sleep-related eating disorder and exploding head syndrome, have unique characteristics that make them distinctly identifiable.

Sleep-Related Eating Disorder

Sleep-related eating disorder is not officially classified among the disorders of arousal, although it shares many characteristics with them and might be a variant of sleepwalking. Sleep-related eating disorder is characterized by episodes of involuntary eating at the time of the main sleep period, during periods of altered consciousness and not full wakefulness[1]; this feature is in contrast to night eating syndrome, an eating disorder in which patients are fully awake and consume excessive calories at night.[15,16] Similar to the disorders of arousal, recall for sleep-related eating disorder events tends to be limited. The substances consumed by someone with sleep-related eating disorder might not be edible, such as cleaning products or paper. Furthermore, if the individual engages in food preparation during an altered state of consciousness, they may have an increased risk of burn or other injury from cooking. To meet diagnostic criteria for sleep-related eating disorder, the sleep-related eating must be associated with behavior that has adverse health consequences. Eating disorders, particularly those requiring hospitalization, have also been associated with sleep-related eating disorder.[17]

Exploding Head Syndrome

Exploding head syndrome is characterized by the sudden sensation of a loud noise in the head during the transition from wake to sleep or during middle-of-the-night awakenings.[1] These noises are startling and unpleasant sensations that cause abrupt arousal, with no associated pain. In some cases, the sounds will

TABLE 6-1 **Clinical Features That Help Distinguish Non–Rapid Eye Movement From Rapid Eye Movement Sleep Parasomnias**

	Non-REM sleep parasomnias	REM sleep parasomnias
Timing	First third of the night	Second half of the night
Recall	Poor	Often vivid
Activity	Rarely violent	Can be violent
Cognitive status immediately following event	Confused	Alert
Age	Younger	Typically ≥60 years (with exceptions)
Family history	Common	Seldom

REM = rapid eye movement.

recur multiple times as the patient attempts to fall asleep. While no known directly harmful consequences of exploding head syndrome occur, their repeated occurrence can affect one's ability to fall asleep and lead to psychological distress and insomnia. Exploding head syndrome has been described in medical literature for over 100 years,[18] with an estimated prevalence of over 11% in adults.[19] Intriguingly, EEG studies suggest that people with exploding head syndrome are drowsy or awake rather than fully asleep when their symptoms occur,[20] making exploding head syndrome's classification as a non-REM parasomnia debatable; however, exploding head syndrome is currently considered to be a non-REM parasomnia as the entity is not better classified elsewhere at this time.

DIFFERENTIAL DIAGNOSIS

When an adult patient presents with abnormal sleep-related behaviors, the key questions are whether the events arise out of non-REM or REM sleep and if the events represent seizures. Common clinical features that may help to differentiate non-REM from REM parasomnias are listed in TABLE 6-1. In clinical practice, differentiating sleep terrors from REM sleep behavior disorder can be difficult, especially for patients who awaken with a memory of dreamlike mentation that occurred during their sleep terrors. Typically, non-REM parasomnias occur earlier in the night than REM parasomnias and are less frequently associated with vivid dream imagery and dream recall. It is also possible for patients to experience both REM and non-REM parasomnias, referred to informally as parasomnia overlap disorder.[21] Although the clinical history may help to differentiate non-REM from REM parasomnias, the definitive distinction requires capturing an event on a polysomnogram or video EEG to establish the stage of sleep from which the events arise.

Nocturnal frontal lobe epilepsy can manifest as "agitated somnambulism," distinguished from primary sleepwalking with an EEG that captures the event and identifies epileptic discharges arising from stage N1 or N2 sleep rather than an arousal from stage N3.[22] The Frontal Lobe Epilepsy and Parasomnias scale has been proposed for assisting in differentiating the two conditions, but its use in clinical sleep practice is discouraged due to concerns about misdiagnosis.

Another step in the evaluation and management of suspected non-REM parasomnia is to determine if the non-REM parasomnia events are primary, or secondary to another sleep or medical condition, including substance abuse or prescription medications. This clinical distinction affects treatment planning since therapy for non-REM parasomnia secondary to another sleep or medical condition would start with treatment of the underlying condition, removal of the offending agent, or both. A primary parasomnia should only be diagnosed when secondary causes are excluded. Few medications have been associated with the development of non-REM parasomnias (TABLE 6-2), and to be considered a parasomnia due to medication a temporal link must exist between the two.[23] Whether the use of any particular illicit substances increases the risk of non-REM parasomnias is unknown.

Medical disorders, particularly other sleep disorders, can present with parasomnias and should be on the differential diagnosis for any patient presenting with abnormal sleep behaviors. Restless legs syndrome, for example, has been associated with sleep-related eating disorder, possibly related to the increased drive to get up and move during the night.[24] A possible association between obstructive sleep apnea and sleepwalking also exists, with at least one

KEY POINTS

- Sexsomnia is a rare but socially disturbing form of confusional arousal in which patients partially awaken and perform sexual acts without awareness or memory.
- Sleep-related eating disorder is characterized by high-volume, high-calorie, or unsafe eating in an altered state of consciousness during the night.
- Exploding head syndrome is characterized by the sudden sensation of a loud noise in the head during the transition from wake to sleep.
- Typically, non–rapid eye movement (REM) parasomnias occur earlier in the night than REM parasomnias and are less frequently associated with vivid dream imagery and dream recall.
- Nocturnal frontal lobe epilepsy can manifest as "agitated somnambulism," distinguished from primary sleepwalking with an EEG that captures the event and identifies epileptic discharges arising from stage N1 or N2 sleep rather than an arousal from stage N3.
- Non-REM parasomnias are frequently encountered in a familial pattern, which suggests that a genetic predisposition is likely.
- Non-REM parasomnias arise mostly from stage N3 sleep rather than stages N1 or N2, likely because the arousal threshold from stage N3 is greater and there is more potential for a partial or impaired arousal.

study demonstrating that the risk of sleepwalking is positively correlated with the severity of sleep apnea.[24] Patients with restless legs syndrome might also be predisposed to sleepwalking due to the underlying restlessness, although no increase in sleepwalking was found in a large cohort of patients with restless legs syndrome.[26]

PATHOPHYSIOLOGY

The underlying causes of disorders of arousal (including sleep-related eating disorder) are not well understood and, compared to many other sleep disorders, not extensively studied. Even less is known about the etiology of exploding head syndrome. Disorders of arousal likely have a genetic basis. Evidence for this hypothesis comes from the high rates of positive family history of non-REM parasomnia.[27] One of the largest studies to date showed a high prevalence of the human leukocyte antigen DQB1*05:01 genotype among patients with sleepwalking and sleep terrors.[28] This finding further supports the notion that the disorders of arousal may be different clinical manifestations of the same underlying pathophysiology rather than distinct disorders.

Non-REM parasomnias arise mostly from stage N3 sleep rather than stages N1 or N2, likely due to the greater arousal threshold from stage N3 and the increased potential for a partial or impaired arousal.[29] Conditions that increase sleepiness and therefore the arousal threshold, such as sleep deprivation and sedative-hypnotic medications, can increase the risk of parasomnias by making it more difficult to fully awaken when aroused.[30,31] By comparison, waking from the "lighter" stages of N1 and N2 sleep is relatively easy.[32] The behavioral episodes themselves are associated with increased delta activity, the hallmark feature of stage N3 sleep, indicating the incomplete electrical transition from sleep to wake.[33] These incomplete transitions tend to be regional, with evidence that the frontal lobes show the least activation with these disordered arousals as would be expected from the lack of executive control often displayed during the events.[34,35] A full description of the neurophysiology of non-REM parasomnias is beyond the scope of this article but can be found in several published reviews on the subject.[30,36,37]

In the context of a high threshold for awakening, any condition that increases the number of arousals may increase the chances of experiencing a disordered arousal.[38] Thus, conditions such as narcolepsy, periodic limb movements of sleep, and sleep-disordered breathing can increase the risk for non-REM

TABLE 6-2 **Drugs Associated With Increased Risk of Non–Rapid Eye Movement Parasomnias**

- Calcium, magnesium, potassium, and sodium oxybate (also known as oxybate salts or low-sodium oxybate)
- Eszopiclone
- Sodium oxybate
- Zaleplon
- Zolpidem
- Zopiclone

parasomnias by fragmenting sleep.[30,39,40] Evidence also exists that treatment of sleep-disordered breathing can reduce parasomnia frequency.[41,42] Sleep-disordered breathing might put patients at particularly high risk of non-REM parasomnias due to the combination of increased sleepiness and sleep fragmentation.

DIAGNOSIS

The diagnosis of non-REM parasomnia can often be made with a thorough history from the patient and, when available, from family members, bed partners, and others who have observed the patient's sleep-related behavior. Polysomnography is not required in most cases and can be unhelpful if the described sleep-related behavior event is not captured. While certain polysomnographic features are observed in studies of disorders of arousal,[43] these features are not considered to be required diagnostic criteria for non-REM parasomnias. If the patient's sleep-related behavior is captured during the study, the contextual aspects of the behavior are assimilated to either support or refute a diagnosis of a non-REM parasomnia. Polysomnography is most beneficial to evaluate for comorbid sleep apnea or periodic limb movement disorder if the clinical history suggests that either of these entities may be potential exacerbators of the non-REM parasomnia. Polysomnography should also be pursued when the differential diagnosis includes sleep-related seizures or REM sleep behavior disorder.

MANAGEMENT

As non-REM parasomnias are not associated with substantial negative health outcomes, the goals of care are to provide an accurate diagnosis, ensure patient safety, and improve quality of life. Comorbid sleep disorders should be treated as part of a comprehensive approach to treating non-REM parasomnias. While some parasomnias (eg, confusional arousals, night terrors, exploding head syndrome) might be medically unharmful, they can be highly disruptive and embarrassing to the patient. Thus, it is best to avoid the term *benign* even in cases where no physical harm is likely to befall the patient.

Safety counseling is paramount for all patients with non-REM parasomnia. Patients, bed partners, and others in the living environment should be educated about the risks of sleepwalking and sleep-related eating disorder, such as physical injuries from falls or other accidents, weight gain, or consumption of inedible substances. TABLE 6-3 provides safety tips for patients

Safety Considerations for Individuals With Non–Rapid Eye Movement Parasomnias TABLE 6-3

- Create a safe sleeping environment by locking windows, removing weapons, and keeping the floor clear of tripping hazards
- Sleepwalkers can generally be guided back to bed without awakening them
- Those likely to get out of bed during an event should avoid sleeping in lofts or upper bunks
- Consider safety gates at the top of stairs for those with upper-floor bedrooms
- Door alarms can be installed and linked to smartphones to alert family members[44]

KEY POINTS

- Increased sleep pressure from sleep deprivation or medications can increase parasomnias by making it more difficult to awaken.
- Sleep fragmentation increases the risk of disordered arousals, which is the suspected mechanism behind the higher risk of non-REM parasomnias among patients with sleep-disordered breathing.
- Accurate diagnosis, patient safety, and improved quality of life are the primary goals of care for patients with non-REM parasomnias.
- Safety counseling and reassurance are the mainstay of treatment for non-REM parasomnias.
- Sleep deprivation should be avoided, as should sedative medications, particularly benzodiazepine receptor agonists (eg, zolpidem).
- While clonazepam is the traditional pharmacologic therapy for non-REM parasomnias, dopamine agonists, gabapentinoids, antidepressants, and melatonin have been found to be effective in some circumstances.
- Scant data exist about the frequency of non-REM parasomnias among different racial and ethnic groups in the United States.
- Sex differences are suspected in the specific cases of sleep-related eating disorder and sexsomnia, with the former being more prevalent in females and the latter being more prevalent in males.

and family members. Patients should be instructed on the importance of consistently obtaining 7 to 9 hours of nocturnal sleep. Sleep deprivation should be avoided, as should sedative medications, particularly benzodiazepine receptor agonists (eg, zolpidem). Another strategy is to schedule an awakening prior to the anticipated onset of the behavioral event. If the non-REM parasomnia occurs around the same time each night, a planned awakening (to full wakefulness) before the usual time of the non-REM parasomnia could prevent the episode.[45]

If the patient's non-REM parasomnia persists despite nonpharmacologic therapy, other treatment modalities may be considered. A retrospective study of patients treated for parasomnias showed that benzodiazepines were among the most effective interventions, with benzodiazepine receptor agonists, antidepressants, and melatonin also demonstrating efficacy, ranging from a 50% to 80% rate of complete or satisfactory resolution of symptoms.[46] Clonazepam is the most commonly prescribed medication for non-REM parasomnia, with patients often responding to doses of 0.5 mg to 1 mg. The seminal study of clonazepam for non-REM parasomnias showed stable dosing and sustained efficacy over long-term follow-up.[46] Dopamine agonists and gabapentinoids also have high rates of success in reducing parasomnias.[45] It is speculated that these drugs improve parasomnias by reducing arousals from periodic limb movements of sleep, but whether these medications work for all patients with parasomnias or just those with underlying periodic limb movements of sleep has not been determined. In the specific case of sleep-related eating disorder, the antiseizure drug topiramate has also demonstrated efficacy.[48] Based on these studies, the use of pharmacotherapy in clinically appropriate patients may satisfactorily reduce the frequency of non-REM parasomnia events. Hypnosis as a treatment for non-REM parasomnia is supported by small trials,[49] but access to this modality may limit its use for many individuals.

HEALTH DISPARITIES AND SOCIAL IMPLICATIONS

Scant data exist about the frequency of non-REM parasomnias among different racial and ethnic groups in the United States. Because racial differences exist in conditions associated with parasomnias, such as obstructive sleep apnea[50] and restless legs syndrome,[51] one might expect to find differences in parasomnias as well, but rates of parasomnias by race have not been examined. Slightly more data exists on sex differences for non-REM parasomnias, which do not suggest a substantial difference in frequency between males and females for most parasomnias (with the possible exceptions of exploding head syndrome, which might have a female predominance and sexsomnia which might have a male predominance).[47,52–54]

Non-REM parasomnias can cause a great deal of distress to both patients and those who sleep near them. Hearing a parent scream in terror can be extremely frightening for young children in the same or nearby bedrooms. Bed partners find their own sleep to be negatively impacted by an individual's frequent nocturnal activity. Non-REM parasomnias can be particularly problematic for patients who travel; their sleep behaviors might embarrass them or impact the sleep of those nearby, and sleeping in an unfamiliar environment may pose safety threats during non-REM parasomnias. Some people will not stay as a guest in a friend's or relative's home. Others cannot travel for work if they are required to share a hotel room with a colleague. Those with sleep-related eating disorder

might find weight gain to be another undesired consequence. As-needed use of pharmacotherapy during episodic travel and room sharing may be considered for those who do not require or desire nightly medication.

Finally, some non-REM parasomnias may have legal implications, mostly sleepwalking. On May 24, 1987, Kenneth Parks of Ontario, Canada drove 14 miles to the home of his mother-in-law and father-in-law and subsequently murdered her and severely wounded him.[55] A year later, he was acquitted by a jury that believed the defense's argument that he had been sleepwalking.

CONCLUSION

Non-REM parasomnias comprise an array of behaviors marked by a hybrid sleep-wake state. While night terrors, sleepwalking, and confusional arousals are grouped separately as disorders of arousal, it is reasonably likely that sleep-related eating disorder exists along the same continuum. Exploding head syndrome, by contrast, is a unique and generally unharmful condition. Non-REM parasomnias, while often thought of as childhood disorders, are relatively common in adults as well. Adults with non-REM parasomnias can experience a variety of negative consequences, including compromised safety, embarrassment, and weight gain. Treatment involves the reduction of exacerbating factors, management of comorbid sleep disorders, safety counseling, reassurance, and, if needed, medication. Treatments are often highly successful, improving quality of life for patients and their families.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders

By Meena Khan, MD, FAASM

ABSTRACT

OBJECTIVE: **This article reviews common sleep-related movement disorders, including their clinical description, epidemiology, pathophysiology (if known), and evaluation and management strategies. This article will provide the reader with a good foundation for approaching concerns that are suggestive of sleep-related movement disorders to properly evaluate and manage these conditions.**

LATEST DEVELOPMENTS: **α2δ Ligands, such as gabapentin enacarbil, can be used for the initial treatment of restless legs syndrome (RLS) or in those who cannot tolerate, or have developed augmentation to, dopamine agonists. Another option is the rotigotine patch, which has a 24-hour treatment window and may be beneficial for those who have developed augmentation with short-acting dopamine agonists. IV iron can improve RLS symptoms even in those whose serum ferritin level is between 75 ng/mL and 100 ng/mL. At serum ferritin levels greater than 75 ng/mL, oral iron will likely have minimal absorption or little effect on the improvement of RLS. Research has found an association between RLS and cardiovascular disease, particularly in people who have periodic limb movements of sleep.**

ESSENTIAL POINTS: **RLS is the most common sleep-related movement disorder. Its pathophysiology is likely a combination of central iron deficiency, dopamine overproduction, and possibly cortical excitation. Treatment includes oral or IV iron. Dopaminergic medications can be very effective but often lead to augmentation, which limits their long-term use. Other sleep-related movement disorders to be aware of are sleep-related rhythmic movement disorder, nocturnal muscle cramps, sleep-related propriospinal myoclonus, sleep bruxism, and benign myoclonus of infancy.**

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INTRODUCTION

Sleep-related movement disorders can be very disruptive to a person's sleep, leading to insomnia, daytime impairment, or both. The most common sleep-related movement disorder is restless legs syndrome (RLS). However, it is important to recognize other sleep-related movement disorders because they are included in the differential

diagnosis and, if present, need to be addressed to optimize a patient's sleep and quality of life.

RESTLESS LEGS SYNDROME

The primary symptom of RLS is an irresistible need to move one's limbs. RLS is a clinical diagnosis based on three criteria noted by the *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*), as shown in TABLE 7-1.[1]

Epidemiology

While many patients describe the sensations of RLS in the legs, 21% to 57% describe this sensation in the arms. The prevalence of RLS is 1.5% to 2.4% in the United States and is twice as high in women than in men; the prevalence also increases with age up to age 65 years.[2-5] Approximately 60% of people with RLS have a family history of the condition.[6] A high concordance rate for RLS is seen in monozygotic twins,[5] and a higher frequency of first-degree relatives with RLS is seen in those with early-onset symptoms (age of onset prior to 45 years old).[7] RLS is associated with significant comorbidities of decreased quality of life, insomnia, major depressive disorder, anxiety, depression (some studies indicate depression is particularly prevalent in older males), attention deficit hyperactivity disorder, and cardiovascular disease.[5,8]

RLS is associated with iron deficiency, pregnancy, and chronic renal failure. The prevalence of RLS in pregnancy is 2 to 3 times that of the general population and increases with each trimester, most often occurring in the third trimester and resolving after the first month following delivery.[5] Having RLS in pregnancy increases the risk of having it in subsequent pregnancies and of developing chronic RLS.[5,9] Medications, particularly antihistamines and serotonergic antidepressants (with the exception of bupropion), can aggravate or even cause RLS.

The genetic component of RLS is mostly consistent with an autosomal dominant pattern with anticipation, meaning that with each generation the

***ICSD-3-TR* Diagnostic Criteria for Restless Legs Syndrome[a]** TABLE 7-1

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria A through C must be met for a restless legs syndrome diagnosis:**

A An urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. The symptoms must:

1 begin or worsen with rest or inactivity such as lying down or sitting,

2 be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and

3 occur exclusively or predominantly in the evening or night rather than during the day.

B The symptoms listed above are not solely accounted for by a condition that mimics restless legs syndrome (eg, leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping).

C The symptoms cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

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condition can start earlier and be more severe.[6] Genome-wide association studies have found associations between RLS and the genes *PTPRD*, *BTBD9*, *MEIS1*, *MAP2K5*, *SKOR1*, and *TOX3*.[6]

Pathophysiology

RLS is associated with iron deficiency, and iron repletion can improve RLS symptoms. Conditions that contribute to low iron, such as renal disease and pregnancy, are associated with an increased risk for RLS. While low peripheral iron can lead to RLS, patients' iron studies are often normal, indicating that there may be an iron deficiency in the central nervous system. MRI brain studies of patients with RLS have shown regional iron deficiencies in the substantia nigra, putamen, caudate, and thalamus.[10,11] Low iron is also seen in the CSF of people with RLS.[12-14] These iron deficiencies may be due to impaired transport of iron into the brain, particularly in the neuromelanin cells of the substantia nigra. Central iron deficiency may lead to the activation of hypoxic pathways and mild myelin deficit, as iron is needed to produce myelin.[10]

People with RLS experience robust symptomatic improvement with the use of dopaminergic medications, which raises the question about potential dopamine deficiency in the setting of RLS. However, studies show the opposite to be true, with downregulation of dopamine D2 receptors seen in people with RLS. One theory about dopamine's role in RLS pathogenesis is that dopamine production has a circadian rhythm, with decreased production in the evening. As such, the decrease in D2 receptors is balanced during the day, but at night the decreased dopamine production leads to a relative dopamine deficiency that causes RLS symptoms.[10]

Dopaminergic medications initially correct this relative deficiency but ultimately enhance the downregulation of dopamine receptors, which then leads to worsening symptoms and augmentation over time. Other theories of cortical excitability and descending dopaminergic spinal pathways in RLS have been postulated but require further study.[10]

Evaluation

Once a diagnosis of RLS is established using the *ICSD-3-TR* criteria, understanding the extent to which the RLS symptoms affect the person's ability to sleep and function is important. The International RLS Study Group developed the International RLS Study Group Rating Scale, which is a validated ten-item questionnaire to rate the severity of RLS and its impact on the respondent's life.[15] Each question has a rating of 0 to 4, with 0 being "not affected" and 4 being "very severe." A total score of 1 to 10 is mild, 11 to 20 is moderate, 21 to 30 is severe, and 31 to 40 is very severe.[15] The International RLS Study Group Rating Scale is self-administered and can be given at the time of the initial consultation and longitudinally throughout the treatment course to gauge how symptom severity changes over time and in response to intervention.

Screening for RLS consists of evaluating the patient for potential conditions that can cause RLS as well as screening for other conditions that may present similarly to RLS such as nocturnal leg cramps, venous stasis, arthritis, or myalgias.

The use of antidepressants can be associated with the development or worsening of RLS.[16] Tapering off or discontinuing antidepressants or dopamine receptor antagonists (eg, antipsychotic medications) should be discussed and considered, if feasible.

Serum ferritin levels (ideally obtained after fasting and in the morning) and transferrin saturation percentage should be checked as part of the initial evaluation. If the serum ferritin level is less than 75 ng/mL or if transferrin saturation is less than 20% to 25%, iron therapy should be started. Ferritin is an acute-phase reactant and may be falsely high in certain conditions such as liver disease or inflammatory disease, so correlating ferritin level with transferrin saturation is important for verification. Iron supplementation should still be considered if the serum ferritin level is greater than or equal to 75 ng/mL and the transferrin saturation is less than 20% to 25%.[17]

Treatment

Various treatment options are available for RLS. These include iron supplementation, pharmacological treatment, and nonpharmacologic interventions.

IRON REPLACEMENT THERAPY. Iron supplementation should be prescribed if the serum ferritin level is less than 75 ng/mL, the transferrin saturation is less than 20% to 25%, or both. The recommended dose is 65 mg of elemental iron, twice a day 1 hour before a meal.[17] Ferrous sulfate 325 mg, twice daily, is the most common form of oral iron used, although ferrous fumarate can also be used. This can be combined with 100 mg to 200 mg of vitamin C for better absorption.[17-19] Gastrointestinal adverse effects from oral iron include nausea and constipation. Oral iron may help mild RLS symptoms but may not be effective for severe RLS. If oral iron is not tolerated or effective, IV iron can be considered. Low-molecular-weight iron dextran is recommended due to the low risk of anaphylaxis.[17,19,20] Symptom improvement with IV iron can occur after 2 to 4 weeks but could take up to 6 weeks.[17,19] Of the low-molecular-weight IV iron formulations available, ferric carboxymaltose 1000 mg infused over 1 hour has the most evidence for the treatment of RLS, is considered first-line treatment, and has been shown to improve RLS symptoms in those with serum ferritin levels less than 100 ng/mL and transferrin saturation less than 45%.[19] Other formulations such as IV iron sucrose and low-molecular-weight iron dextran can be used but have less evidence for efficacy.[19] Serum ferritin levels and transferrin saturation should be reassessed 12 weeks posttreatment with oral iron and 8 to 16 weeks posttreatment with IV iron.[19] CASE 7-1 illustrates how iron supplementation is incorporated into RLS treatment.

DOPAMINERGIC MEDICATIONS. Dopamine agonists are commonly prescribed for RLS treatment. The US Food and Drug Administration (FDA)-approved dopamine agonist medications for RLS are oral pramipexole, oral ropinirole, and the rotigotine patch. While these medications are very effective in the short term, augmentation is a risk in the long term.

Augmentation is the worsening of RLS symptoms in response to medication and is often seen with the use of dopaminergic medications. This increase in RLS symptom intensity occurs after an increase in medication dose and decreases in response to a decrease in the medication dose.[3] Typically, augmentation presents as an earlier time of RLS symptom onset, the movement of symptoms to other limbs, and a shorter treatment effect window compared with when the treatment started. Increases in the dose of a dopaminergic medication can lead to further augmentation; therefore, it is recommended to use lower doses of these

KEY POINTS

- The prevalence of restless legs syndrome (RLS) in pregnancy is 2 to 3 times that of the general population and increases with each trimester, most often occurring in the third trimester and resolving after the first month following delivery.
- Tapering off or discontinuing antidepressants or dopamine receptor antagonists (eg, antipsychotic medications) should be discussed and considered in patients with RLS, if feasible.
- Evaluation for RLS should include checking serum ferritin levels and transferrin saturation. If serum ferritin is less than 75 ng/mL or if transferrin saturation is less than 20% to 25%, iron therapy should be considered including IV iron if the patient cannot tolerate oral iron.
- Dopamine agonists and α2δ ligands are US Food and Drug Administration (FDA)-approved for the treatment of RLS. Patients on dopamine agonist therapy should be monitored for augmentation and impulse control symptoms.
- Opioids can be effective for RLS treatment and are typically used when other management strategies have failed.
- Lifestyle changes such as reducing or eliminating caffeine and alcohol can help with RLS symptom management.

medications (TABLE 7-2). Carbidopa/levodopa can effectively treat RLS, but a high rate of augmentation risk (60%) means that dopamine agonists are typically favored.[17] The rotigotine patch releases dopaminergic agonistic activity over 24 hours and provides day-long coverage, which may lead to a lower risk of augmentation.[21] The rotigotine patch is changed daily and the location should be different each time to minimize skin reaction, redness, or itching; the same site should not be used again for 14 days. The patch can be placed on the upper arms, legs, scapula, or upper back.[17] Impulse control disorders, such as excessive spending, shopping, or gambling, can develop in 15% of patients taking dopamine agonists.[17] Sleep attacks are also a possible adverse effect of this medication class.[22]

Augmentation can be difficult to manage. Some studies show that the risk of augmentation is higher for short-acting versus long-acting dopamine agonists, but were inconclusive.[23] However, a long-acting formulation is a reasonable treatment option to consider in someone who has developed augmentation to a short-acting dopamine agonist if other mediation classes such as α2δ ligands are not viable options (CASE 7-2). The only FDA-approved 24-hour formulation for RLS is the rotigotine patch. The long-acting forms of pramipexole and ropinirole

CASE 7-1

A 45-year-old woman presented with an uncomfortable sensation of needing to move her legs, which had been occurring for the past year. This sensation often occurred when she was laying down to go to sleep at night. Her leg discomfort improved if she moved her legs or got up to walk around, but then reoccurred when she laid down again. The cycle of getting up to relieve her leg discomfort caused her to remain awake for 1 to 2 hours before she fell asleep and occurred two to three times per week. Her serum ferritin level was 30 ng/mL, and she started ferrous sulfate 325 mg twice daily, with vitamin C 100 mg once daily. After a couple of weeks, she discontinued iron therapy due to constipation and nausea. She then tried pramipexole and developed a habit of compulsive online shopping, potentially indicating impulse control disorder. She did not want to try gabapentin because she was concerned about potential side effects. She was subsequently referred to a hematologist to consider IV iron. She had one infusion of ferric carboxymaltose 1000 mg and her restless legs syndrome (RLS) symptoms improved after 2 to 3 weeks. Her serum ferritin level was measured at 8 weeks. Her ferritin level had increased to 150 ng/mL and her RLS symptoms had resolved.

COMMENT

This case illustrates the management options for a person with RLS who was unable to use dopamine agonists or α2δ ligands and had a low serum ferritin level. She was unable to tolerate oral iron so she was given IV iron, which improved her RLS symptoms. As this case shows, IV iron can be especially helpful when serum ferritin is below goal and other RLS treatment options have been exhausted. At times, neurologists may need to collaborate with hematologists to obtain insurance approval for the use of IV iron in people who have RLS and low serum ferritin levels but do not have anemia.

are not FDA approved for RLS and may not be covered by insurance, making them too costly for many individuals. The maximum dose of rotigotine recommended for RLS is 3 mg every 24 hours.

α2δ LIGANDS. Gabapentin enacarbil is an α2δ ligand that is FDA approved for the treatment of RLS at a dose of 600 mg per day. Pregabalin 300 mg is equally effective as pramipexole for the treatment of RLS and has less risk of augmentation[24,25]; evidence also supports gabapentin as a treatment for RLS. These medications can be taken 1 to 2 hours before RLS symptom onset.[18] Adverse effects of α2δ ligands include dizziness, sedation, and weight gain; for some individuals, these effects may limit their ability to use these medications at the most effective doses. Gabapentin enacarbil has better gastrointestinal absorption compared with gabapentin, but it can also be more expensive with variable insurance coverage. α2δ Ligands are renally cleared in unchanged form and doses may need to be adjusted based on renal function (eg, lower doses in people with renal insufficiency). TABLE 7-2 shows dosage recommendations for α2δ ligands.

OPIOIDS. Opioids can be effective for RLS treatment and are typically used when other management strategies have failed. If opioids are used, an opioid-risk tool should be used to screen for abuse potential. Opioid-risk tools are brief, self-administered screening tools used to assess a patient's risk for opioid abuse. Other clinical monitoring strategies include an opioid use contract, urine toxicology

Medications for Restless Legs Syndrome TABLE 7-2

Medication	Dosing regimen	Titration
Dopamine agonists		
Pramipexole	0.25 mg 2 to 3 hours before sleep to a maximum dose of 0.5 mg daily	Start at 0.125 mg a day; can increase by 0.125 mg a week to a max dose of 0.5 mg daily
Ropinirole	0.25 mg to 3 mg to 4 mg 1 to 3 hours before symptom onset	Start at 0.25 mg a night; can increase by 0.25 mg to 0.5 mg a week to a max dose of 3 mg to 4 mg daily
Rotigotine patch	1 mg to 3 mg every 24 hours	Start at 1 mg every 24 hours and can increase by 1 mg a week to a max dose of 3 mg every 24 hours
α2δ Ligands		
Gabapentin enacarbil	600 mg at 5 PM daily	FDA-approved dose is 600 mg a day
Pregabalin	150 mg to 450 mg per day 1 to 3 hours before restless legs syndrome (RLS) symptom onset	Consider starting at a lower dose of 50 mg a day and increase by 75 mg to 150 mg a week to goal dose of 300 mg a day; can go up to a dose of 450 mg daily for RLS
Gabapentin	300 mg 1 to 3 hours before RLS symptom onset	Start at 300 mg a day and can go up by 300 mg a week to 1200 mg to 2400 mg daily; this can also be used in split dosing of 2 to 3 times a day for those with daytime RLS symptoms; better absorption with multiple doses (not more than 600 mg/dose) spaced ≥2 hours apart

FDA = US Food and Drug Administration.

screenings, regular follow-up appointments, and review of prescription monitoring program reports, if available. Prescription monitoring programs collect information on the dispensation of controlled substances to patients. Opioid options include tramadol 50 mg/day to 200 mg/day, codeine 30 mg/day to 180 mg/day, oxycodone 10 mg/day to 30 mg/day, methadone 2.5 mg/day to 20 mg/day, and buprenorphine hydrochloride/naloxone (sublingual film or tablet) 0.5 mg/day to 6 mg/day.[18] These medications can be divided into split dosing throughout the day. Long-acting opioids may be more beneficial than short-acting opioids.

NONPHARMACOLOGIC INTERVENTIONS. Lifestyle changes such as reducing or eliminating caffeine and alcohol can help with RLS symptom management. Massage, stretching, walking, and cognitive distraction (ie, working on a task that requires concentration) are other nonpharmacologic treatment options for people with RLS.[17]

Pneumatic compression devices are commercially available devices that apply compression or other forms of counterstimulation to the legs. These devices have been shown to decrease RLS symptoms in a case series and a randomized sham-controlled trial.[26,27] Using the device for 1 hour a day at the time of symptom onset demonstrated improvement as measured by the International RLS Study Group Rating Scale, the Epworth Sleepiness Scale, and other quality-of-life measures.[27] Individuals may incur an out-of-pocket expense to purchase these devices.

Repetitive transcranial magnetic stimulation over the supplementary motor cortex has been shown to improve the motor symptoms of Parkinson disease and has been found to stimulate dopamine release from the basal ganglia.[28-30]

CASE 7-2

A 55-year-old man with restless legs syndrome (RLS) for many years initially had good treatment benefit with pramipexole 0.125 mg daily, but over time, his RLS symptoms worsened, necessitating an increased dose of pramipexole. His RLS symptoms subsequently began earlier in the day and in his arms, which prompted a dose change to pramipexole 1 mg, twice per day. His medication was then changed to ropinirole, but this was not effective. Serum iron studies showed a serum ferritin level of 80 ng/mL and transferrin saturation of 30%. He tried gabapentin enacarbil, but it caused daytime sleepiness that impaired his daytime function. The extended-release forms of both pramipexole and ropinirole were expensive and not covered by his insurance plan. The rotigotine patch 1 mg/24 hours once daily was prescribed and incrementally increased to 3 mg/24 hours once daily; this was ultimately the dose that controlled the patient's RLS symptoms without medication side effects.

COMMENT

This is an example of augmentation that developed after treatment with a dopamine agonist. Alternative treatments were either ineffective, expensive, or produced intolerable adverse effects.

A randomized study that compared repetitive transcranial magnetic stimulation to sham treatment in 11 people with RLS showed an improvement in International RLS Study Group Rating Scale scores in the intervention group.[31]

A review of 11 randomized controlled trials of nonpharmacologic interventions for RLS[32,33] showed a significant reduction in International RLS Study Group Rating Scale scores with the use of repetitive transcranial magnetic stimulation, a combination of exercise and lifestyle education, pneumatic compression devices, acupuncture, counterstrain manipulation (moving body or limbs that are affected by pain or tension to a position that reduces the pain or tension for 90 seconds, then returning it to neutral), and infrared therapy. Subjective sleep quality was better with vibration pads applied to the calf, yoga exercises, pneumatic compression devices, and standardized acupuncture.

PERIODIC LIMB MOVEMENT DISORDER

Periodic limb movements of sleep are characterized by stereotyped, repetitive limb movements (mostly of the lower extremities) during sleep. Typical movements are extension of the big toe, dorsiflexion of the ankle, flexion of the knee, and sometimes flexion of the hip.[34] Periodic limb movement disorder is a condition defined by periodic limb movements of sleep demonstrated on a polysomnogram and symptoms of sleep disruption or daytime impairment not attributed to a mood disorder or other sleep disorder (eg, obstructive sleep apnea, RLS, rapid eye movement [REM] sleep behavior disorder, narcolepsy). Periodic limb movements of sleep can be associated with sleep arousals, but associated arousals do not always occur, and most patients are not aware that they have limb movements during sleep. Periodic limb movements of sleep are often seen in patients with RLS, narcolepsy, obstructive sleep apnea, and REM sleep behavior disorder.[34]

A diagnosis of periodic limb movements of sleep involves the periodic limb movement index (the number of periodic limb movements recorded, divided by the total sleep time in hours) derived from the polysomnogram. A periodic limb movement index greater than 5 per hour in children and greater than 15 per hour in adults is consistent with periodic limb movements of sleep. Many times, patients have periodic limb movements of sleep but no associated symptoms of sleep disruption or daytime impairment and therefore do not have periodic limb movement disorder. Periodic limb movements of sleep occur in 80% to 90% of those with RLS; however, RLS is a clinical diagnosis based on symptoms and does not require confirmation with a polysomnogram, while a diagnosis of periodic limb movements of sleep is based on a polysomnogram.

A periodic limb movement index greater than 15 per hour has been associated with incident myocardial infarction in men age 65 years and older (mean age of 76 years).[35]

The diagnostic criteria for periodic limb movement disorder are listed in TABLE 7-3.[36]

While the prevalence of periodic limb movement disorder is unknown, the prevalence of periodic limb movements of sleep is thought to be 7.6% in adults up to 65 years old and up to 45% in those over 65 years old.[34] Periodic limb movements of sleep are rare in the pediatric population.

Evaluation and Management

Periodic limb movement disorder is a rare disorder with no evidence-based treatment recommendations. Studies have shown that periodic limb movements

KEY POINTS

- Periodic limb movements of sleep are repetitive movements of the lower extremities seen on a polysomnogram. They can be associated with other sleep disorders.
- Periodic limb movement disorder is defined by periodic limb movements of sleep on a polysomnogram that lead to daytime consequences in the absence of other sleep disorders.
- Periodic limb movements of sleep can be associated with sleep arousals, but associated arousals do not always occur, and most patients are not aware that they have limb movements during sleep.
- Periodic limb movement disorder treatments include dopamine agonists, gabapentin, and pregabalin.
- Sleep-related rhythmic movement disorder can be seen in children with and without autism spectrum disorder and other neuropsychiatric disorders.
- Sleep-related rhythmic movement disorder typically begins around age 9 months and improves with age. Most cases resolve by age 10 years.
- Secondary causes of nocturnal muscle cramps include medications, metabolic disorders, hypokalemia, hypocalcemia, hypomagnesemia, peripheral neuropathy, cardiovascular disease, cirrhosis, uremia, hypothyroidism, venous insufficiency, Parkinson disease, and multiple sclerosis.

of sleep decrease in people with RLS when dopamine agonists, gabapentin, or pregabalin are used.[16] As noted, those with RLS are a distinct cohort from those with periodic limb movement disorder.

SLEEP-RELATED RHYTHMIC MOVEMENT DISORDER

Sleep-related rhythmic movement disorder is characterized by the stereotypic and repetitive movement of large muscle groups that occurs during quiet wakefulness, drowsiness, or sleep. The movements cause vestibular stimulation and may be self-soothing to aid in falling asleep. Sleep-related rhythmic movement disorder is typically seen in children and is only considered a disorder if the movement leads to consequences such as sleep disruption, daytime sleepiness, or injury.[37] Sleep-related rhythmic movement disorder is seen in children with and without autism spectrum disorder or other neurodevelopmental or psychiatric disorders.[38] Sleep-related rhythmic movement disorder has also been associated with attention deficit hyperactivity disorder.[39]

The diagnostic criteria for sleep-related rhythmic movement disorder are listed in TABLE 7-4.[40]

Different types of sleep-related rhythmic movement disorders include body rocking, body rolling, head banging, head rolling, leg banging, and leg rolling (CASE 7-3). Sleep-related rhythmic movement disorder can occur in all stages of sleep but the movement duration is longer in waking periods and sleep stage N1 and shorter in sleep stages N2, N3, and REM.[38] In adults, sleep-related rhythmic movement disorder occurs in REM sleep only.[41]

The average age of onset of sleep-related rhythmic movement disorder is 9 months, with a prevalence of 66% in 9-month-old infants, 8% in 4-year-old children, and 5% in 5-year-old children. Most cases of sleep-related rhythmic movement disorder resolve by age 10 years.[37,41] Sleep-related rhythmic movement disorder rarely starts in adolescence or adulthood, but it can persist into adulthood in a small percentage of patients. Sleep-related rhythmic

TABLE 7-3

ICSD-3-TR Diagnostic Criteria for Periodic Limb Movement Disorder[a]

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria A through D must be met for a periodic limb movement disorder diagnosis:**

A Polysomnography demonstrates periodic limb movements during sleep as defined in the latest version of the *American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events*.

B The frequency is greater than 5 per hour for children and greater than 15 per hour for adults.

C The periodic limb movements of sleep cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

D The periodic limb movements of sleep and symptoms are not explained by another current sleep disorder, medical disorder, or mental disorder (eg, periodic limb movements of sleep occurring with apneas, hypopneas, and respiratory effort-related arousals should not be scored).

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ICSD-3-TR Diagnostic Criteria for Sleep-Related Rhythmic Movement Disorder[a]

TABLE 7-4

International Classification of Sleep Disorders, Third Edition, Text Revision **diagnostic criteria A through D must be met for a sleep-related rhythmic movement disorder diagnosis:**

A **The patient exhibits repetitive, stereotypic, and rhythmic motor behavior involving large muscle groups.**

B **The movements are predominantly sleep related, occurring near naptime, bedtime, or when the individual is drowsy or asleep.**

C **The behaviors result in at least one of the following:**

1 Interference with normal sleep

2 Significant impairment in daytime function

3 Self-inflicted bodily injury or likelihood of injury if preventive measures are not used

D **The rhythmic movements are not better explained by another movement disorder or epilepsy.**

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CASE 7-3

The parents of a 6-month-old boy presented with concern about their baby's sleep-related movement behavior. The parents had recently started to hear noises from the baby monitor after putting him down for the night in his crib; he would lift his head and bang it down on the mattress several times. When the parents checked in, it was clear that he was not distressed or upset and would smile or laugh. The movements stopped fully once he was asleep and, in the morning, he did not seem irritated or upset. The infant ate well, gained weight, and met all developmental milestones on time. The mother's pregnancy was normal with no complications at delivery. The parents saw no bruises or other indications of injury from the sleep-related movements but were concerned about potential injury and the developmental implications of the movements.

To address the parents' concerns, the boy's neurologist explained that this was a sleep-related movement with no developmental consequences. The parents were reassured that the infant was neurologically and developmentally normal and would likely outgrow this behavior. To help minimize sleep-related movement, the parents were educated on keeping the sleeping environment safe for the infant and maintaining a consistent bedtime routine.

COMMENT

This case describes head banging, which is a type of sleep-related rhythmic movement disorder. The infant was neurologically and developmentally normal and not distressed by the movements.

movement disorder occurs equally in male and female children but has a higher prevalence in adult males.[41]

Evaluation and Management

Sleep-related rhythmic movement disorder is a clinical diagnosis based on fulfilling the *ICSD-3-TR* criteria. The differential diagnosis of sleep-related rhythmic movement disorder includes seizures, parasomnias, and other sleep-related movement disorders.[38] Most cases of sleep-related rhythmic movement disorder resolve spontaneously before adulthood and do not affect sleep quality. If sleep-related rhythmic movement disorder results in injury or impairment in daytime functions (which can occur in adulthood), case reports describe using medications such as clonazepam and melatonin.[42,43] Other management strategies for sleep-related rhythmic movement disorder include optimization of sleep hygiene and sleep habits in addition to treating other comorbid sleep disorders (eg, obstructive sleep apnea, RLS).[44-46] Hypnosis was shown to be helpful in a single case report.[47]

NOCTURNAL MUSCLE CRAMPS

Nocturnal muscle cramps are characterized by a painful sensation in the leg (mainly the calf) or foot associated with involuntary muscle hardness that occurs in bed and is relieved by stretching. Nocturnal muscle cramps can occur during waking periods or sleep and typically last several minutes.

The diagnostic criteria for nocturnal muscle cramps are listed in TABLE 7-5.[48]

Nocturnal muscle cramps are seen in 50% to 60% of adults (prevalence can increase with age)[37,49] and 7.3% of children.[50] Secondary causes of nocturnal muscle cramps include medications, metabolic disorders, hypokalemia, hypocalcemia, hypomagnesemia, peripheral neuropathy, cardiovascular disease, cirrhosis, uremia, hypothyroidism, venous insufficiency, Parkinson disease, and multiple sclerosis.[37,49] A study found that using quinine (a medicine often used to treat leg cramps) was associated with the initial prescription of medication classes such as β-agonists, potassium-sparing diuretics, and thiazide-like diuretics, which suggests that these medications may contribute to nocturnal muscle cramps.[51] Pregnancy may be related to nocturnal muscle cramps, with a reported 30% to 40% estimated prevalence of nocturnal muscle cramps occurring during pregnancy and resolving after delivery.[52]

TABLE 7-5 ***ICSD-3-TR* Diagnostic Criteria for Nocturnal Muscle Cramps**[a]

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria A through C must be met for a nocturnal muscle cramps diagnosis:**

A A painful sensation in a muscle associated with sudden, involuntary muscle hardness or tightness, indicating a strong muscle contraction.

B The painful muscle contractions occur when in bed, although they may arise from either wakefulness or sleep.

C The pain can be relieved by forceful stretching of the affected muscles, thus releasing the contraction.

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Evaluation and Management

Evaluation includes identification of possible inciting medications or medical conditions (eg, vascular insufficiency, radiculopathy, peripheral neuropathy) and checking electrolytes (eg, sodium, potassium, calcium, magnesium).[37] Quinine was commonly used to treat nocturnal muscle cramps, but in 2012 the FDA deemed that quinine should only be used for the treatment of malaria due to the possible adverse effects of thrombocytopenia, hypersensitivity reactions, and QT prolongation.[49] Unfortunately, scant literature supports other medications or supplements for nocturnal muscle cramps. Magnesium supplementation may provide some benefit in pregnant women but not nonpregnant adults.[53] Behavioral treatment such as leg stretching may be beneficial for nocturnal muscle cramps but requires further study.[54]

SLEEP-RELATED BRUXISM

Bruxism is characterized by repetitive jaw movements that lead to clenching or grinding of the teeth by thrusting the mandible and can occur during sleep or waking periods. Patients may not suffer from disrupted sleep due to bruxism, but their bed partner may be bothered by the grinding noise. Jaw contractions that occur repeatedly during sleep are called rhythmic masticatory muscle activity. Rhythmic masticatory muscle activity can occur in people without sleep complaints; if it leads to grinding sounds or tooth damage, it is diagnosed as sleep bruxism. Sleep bruxism can lead to tooth pain, tooth wear, jaw pain, and headache.

The diagnostic criteria for sleep-related bruxism are listed in TABLE 7-6.[55]

Sleep-related bruxism occurs in 8% to 13% of the general population and is more common in children than older adults.[56] Sleep-related bruxism occurs due to the activation of the central nervous system as opposed to dental occlusal issues.[57] Risk factors that can contribute to sleep-related bruxism include tobacco and alcohol use, caffeine, stress, anxiety, and disorders causing arousals from sleep such as obstructive sleep apnea, parasomnias, and gastroesophageal reflux disorder.[58,59]

Evaluation and Management

The diagnosis of sleep-related bruxism can be made clinically, as outlined by the *ICSD-3-TR* and by polysomnography. Polysomnograms typically show bruxism

***ICSD-3-TR* Diagnostic Criteria for Sleep-Related Bruxism[a]** TABLE 7-6

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria**
A and B must be met for a sleep-related bruxism diagnosis:

A **The presence of repetitive jaw-muscle activity characterized by grinding or clenching of the teeth in sleep.**

B **The presence of one or more of the following clinical symptoms or signs consistent with the above reports of tooth grinding or clenching during sleep:**

1 Abnormal tooth wear

2 Transient morning jaw muscle pain or fatigue, or temporal headache

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KEY POINTS

- Magnesium supplementation may help in pregnant people with leg cramps.
- Sleep-related bruxism is a centrally mediated condition that can cause symptoms of jaw pain, tooth wear, and morning headaches. Disorders that cause arousals from sleep (eg, obstructive sleep apnea) can cause or exacerbate sleep-related bruxism.
- Risk factors that can contribute to sleep-related bruxism include tobacco and alcohol use, caffeine, stress, anxiety, and disorders causing arousals from sleep such as obstructive sleep apnea, parasomnias, and gastroesophageal reflux disorder.
- Sleep-related bruxism can be treated with an oral appliance to decrease tooth damage and by addressing other conditions leading to arousals from sleep.
- Propriospinal myoclonus at sleep onset is characterized by brief truncal muscle jerks that result from signals generated within the thoracic spinal cord that propagate rostrally and caudally.
- Propriospinal myoclonus is typically idiopathic and occurs mainly in middle-aged men, although symptomatic propriospinal myoclonus (propriospinal myoclonus associated with a secondary cause) occurs more in women.

episodes primarily occurring in sleep stages N1 and N2 and least often in the REM stage, and they are associated with arousals from sleep. *The American Academy of Sleep Medicine Scoring Manual, Version 2.6* defines multiple ways to score bruxism on polysomnography[60]:

- Phasic (brief) or tonic (sustained) elevation of chin EMG activity that is at least twice the amplitude of the background EMG
- Brief elevations of chin or masseter EMG activity that are 0.25 to 2 seconds in duration and occur three or more times in a regular sequence (FIGURE 7-1)
- Sustained elevations of chin or masseter EMG activity whose duration is more than 2 seconds
- A period of at least 3 seconds of stable background chin EMG must occur before a new episode of bruxism is scored
- There are at least two audible tooth-grinding episodes per night without epilepsy accounting for the events

Sleep-related bruxism should be treated if the patient is impacted negatively, such as from tooth damage, jaw pain, or disrupted sleep. It is important to address the possible causes listed above and educate the patient on good sleep hygiene to decrease sleep arousals. It is also crucial to treat disorders that may lead to sleep arousal, such as obstructive sleep apnea. If tooth damage occurs, an oral appliance can be created by a qualified dentist. Current evidence does not support the use of medication to treat sleep-related bruxism.[61] Biofeedback has been examined but requires further study.[58]

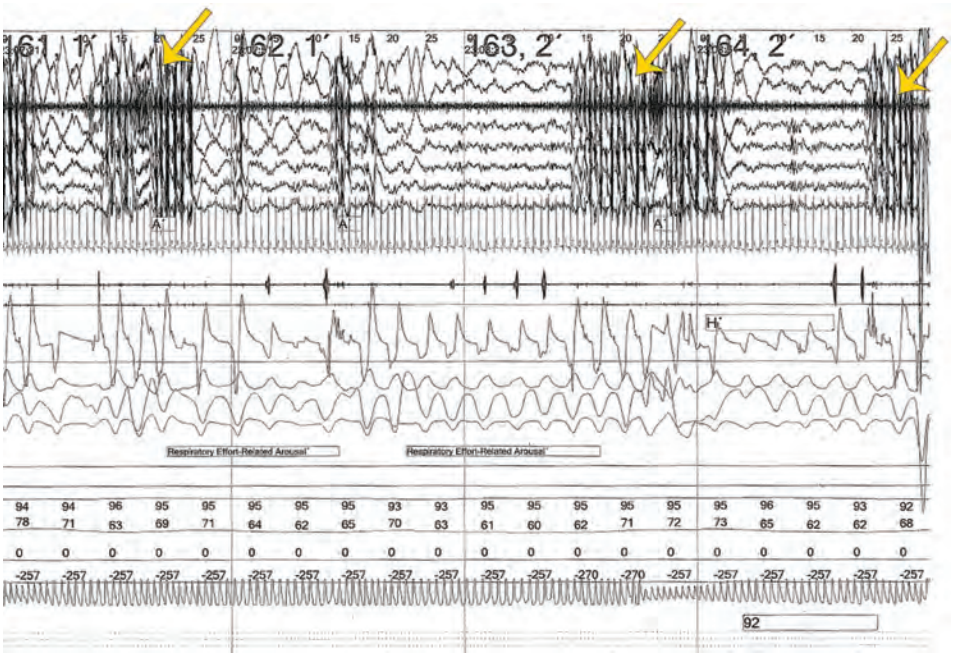

FIGURE 7-1
Bruxism seen on EMG. *Arrows* indicate elevated chin EMG signal occurring during stage N1 and N2 sleep, which is consistent with bruxism.

PROPRIOSPINAL MYOCLONUS AT SLEEP ONSET

Propriospinal myoclonus at sleep onset is characterized by brief muscle jerks that result from signals generated within the spinal cord that propagate up and down the spinal cord beyond a few segments.[37,62] Propriospinal myoclonus is mainly generated in the thoracic spinal cord but can propagate rostrally and caudally.[62] The myoclonus is characterized by repetitive, involuntary jerking of the thoracoabdominal muscles, paraspinal muscles, or both, that leads to flexion (more than extension) of the neck, trunk, or abdomen, and infrequently the upper and lower extremities.[37,63] A somesthetic stimulus, such as tapping on tendons but not by startle, can provoke the myoclonus; at times, the patient may be able to decrease the myoclonic jerks but not completely suppress them via volition or mental activation.[64] Propriospinal myoclonus occurs mostly when laying down to sleep and during wake-to-sleep transitions, which can cause sleep-onset insomnia. Propriospinal myoclonus rarely occurs during arousals in the middle of the night or with waking in the morning and disappears during sleep.[37,62,63]

The diagnostic criteria for propriospinal myoclonus are listed in TABLE 7-7.[65]

Propriospinal myoclonus is typically idiopathic and occurs mainly in middle-aged men, although symptomatic propriospinal myoclonus (propriospinal myoclonus associated with a secondary cause) occurs more in women.[64] Secondary causes of propriospinal myoclonus include infection of the spinal cord, spinal cord trauma, syringomyelia, neoplastic lesions, paraneoplastic conditions, disc herniation, vitamin B_{12} deficiency, celiac disease, and multiple sclerosis.[37,62] Medications such as interferons, ciprofloxacin, and bupivacaine have also been associated with propriospinal myoclonus.[62] Propriospinal myoclonus is rare in children.

Evaluation and Management

The differential diagnosis for propriospinal myoclonus includes myoclonic seizures, truncal dystonias, tics, and hypnic jerks (brief, benign contractions of the body during sleep onset often described as a sense of jerking or falling while falling asleep). Testing can involve polysomnography with extended

***ICSD-3-TR* Diagnostic Criteria for Propriospinal Myoclonus at Sleep Onset[a]** TABLE 7-7

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria**
A through E must be met for a propriospinal myoclonus at sleep onset diagnosis:

A The patient complains of sudden jerks, mainly of the abdomen, trunk, and neck.

B The jerks appear during relaxed wakefulness and drowsiness as the patient attempts to fall asleep.

C The jerks disappear upon mental activation and with the onset of a stable sleep stage.

D The jerks result in difficulty initiating sleep.

E The sleep disturbance is not explained by another current sleep disorder, medical disorder, mental disorder, or medication or substance use.

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EMG using surface electrodes from various paraspinal, neck, and abdominal points and proximal extremity muscle groups.[62] A polysomnogram will show brief EMG bursts consistent with myoclonus occurring when alpha activity is present, and the EMG bursts will disappear as spindles or K complexes appear or the EEG desynchronizes, indicating mental activation.[66] Extended EMG will show myoclonus-related activity that first occurs in muscles innervated by the spinal cord at the cervical or thoracic segments which then travels rostrally and caudally.[66] Imaging of the spinal cord may be appropriate even in the presence of a normal neurologic examination to evaluate for structural abnormalities. Distinguishing psychogenic myoclonus from propriospinal myoclonus may be difficult even with the aforementioned testing.[67] Studies on propriospinal myoclonus treatment are not robust. Clonazepam and botulinum toxin have been shown to improve propriospinal myoclonus.[68] Reports describe propriospinal myoclonus improvement with the use of continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea and propriospinal myoclonus.[69] There are also reports of improvement of propriospinal myoclonus with biofeedback[70] and transcutaneous electrical nerve stimulation.[71]

BENIGN SLEEP MYOCLONUS OF INFANCY

Benign sleep myoclonus of infancy occurs in neonates and infants and is defined as repetitive myoclonic jerks that occur during sleep and resolve with waking. They are often bilateral, involve large muscle groups, and can occur in the trunk, limbs, or face.[72] Infants who experience this are neurologically normal and the myoclonus is self-limited. Onset is typically in the first month of life and resolves by age 1 year.

The diagnostic criteria for benign myoclonus of infancy are listed in TABLE 7-8.[73]

Evaluation and Management

The main alternative diagnosis to consider in this setting is an epileptic seizure. Myoclonus during infancy may not be benign if it occurs during waking periods

TABLE 7-8 ***ICSD-3-TR* Diagnostic Criteria for Benign Sleep Myoclonus of Infancy**[a]

***International Classification of Sleep Disorders, Third Edition, Text Revision* diagnostic criteria A through E must be met for a benign sleep myoclonus of infancy diagnosis:**

- **A** A caregiver or other observer reports repetitive myoclonic jerks that involve the limbs, trunk, or whole body.
- **B** The movements occur in early infancy, typically from birth to age 6 months.
- **C** The movements occur only during sleep.
- **D** The movements stop abruptly and consistently when the infant is aroused.
- **E** The sleep disturbance is not better explained by another current sleep disorder, medical disorder, or medication use.

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or if the infant has an abnormal neurologic examination. EEG can help evaluate myoclonus and will be normal in benign sleep myoclonus of infancy. Video polysomnography in infants with benign sleep myoclonus of infancy will show clusters of myoclonic jerks with four to five jerks per second lasting several seconds, occurring in clusters that last between 1 and 15 minutes or up to 1 hour.[72] The myoclonus mainly occurs during quiet sleep but has been seen in active sleep and always resolves during waking periods.[74] Treatment is not indicated for benign sleep myoclonus of infancy as it will resolve by age 1 year in 97% of cases. In cases that do not resolve by age 1 year, evaluation for seizures should be considered.

CONCLUSION

Sleep-related movement disorders encompass many conditions, ranging from movements with no associated consequence and only require reassurance to movements that cause sleep disruption and daytime impairment. RLS is the most well-known sleep-related movement disorder, with management options that work well for many people, although some symptoms can be challenging to control. Distinguishing periodic limb movements of sleep from RLS is important; periodic limb movements of sleep are diagnosed with a polysomnogram and RLS is a clinical diagnosis. Recognition, evaluation, and management (when indicated) of sleep-related movement disorders can improve patients' sleep and quality of life.

KEY POINTS

- **When assessing for propriospinal myoclonus, imaging of the spinal cord may be appropriate even in the presence of a normal neurologic examination to evaluate for structural abnormalities.**
- **Benign sleep myoclonus of infancy occurs in neonates and infants and is defined as repetitive myoclonic jerks that occur during sleep and resolve with waking.**
- **Benign sleep myoclonus of infancy occurs during sleep only. It can start in the first month of life and resolves by age 1 year in 97% of affected individuals. These infants are neurologically normal and do not have developmental abnormalities.**
- **Patients with benign sleep myoclonus of infancy that does not resolve by age 1 year or has atypical features should be evaluated for epilepsy.**

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Circadian Rhythm Sleep-Wake Disorders

By Flavia B. Consens, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **This article provides an overview of advances in the understanding of circadian rhythms and the health implications of circadian disruption.**

LATEST DEVELOPMENTS: **Circadian medicine is a relatively new concept, with widespread overlap with many other areas of medicine. Circadian clocks rely on feedback loops that control the expression of many genes. Functional circadian oscillators exist at multiple physiologic levels and facilitate a multimodal clock mechanism. The suprachiasmatic nucleus is the central circadian pacemaker. Peripheral tissues can be entrained by other stimuli (such as food intake) and can uncouple from the suprachiasmatic nucleus pacemaker; this discovery may provide new therapeutic options for circadian rhythm disorders. Numerous modern developments have altered our circadian clocks and these changes are associated with poor health outcomes.**

ESSENTIAL POINTS: **Circadian clocks are ubiquitous throughout our body and regulate multiple body functions. Several studies have highlighted that circadian disruption can result in significant negative mental and physical health consequences. A deeper understanding of the effects of misalignment between our circadian clocks and the external environment may ultimately have therapeutic implications for our health.**

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INTRODUCTION

Biological rhythms are ubiquitous. Circadian rhythms are those with a period of approximately 24 hours. Human bodies are also driven by longer periods (such as menstrual periods) or shorter periods, known as ultradian rhythms (such as the distribution of sleep stages throughout the night). The most common rhythms seen in biological organisms are circatidal (12.4 hours), circadian (24 hours), circalunar (29.5 days), and circannual (365.25 days).

Circadian clocks regulate body temperature, hormone secretion, appetite, alertness, and most basic body functions. Growing evidence has demonstrated relationships between circadian disruption and other diseases. Circadian rhythm dysfunction has been associated with poor health outcomes such as cardiovascular disease, neoplastic disease, mental health disorders, and metabolic changes. Misalignment between circadian clocks and environmental cues can lead to circadian rhythm sleep-wake disorders.

CIRCADIAN PHYSIOLOGY

The suprachiasmatic nucleus follows a diurnal (or daily) cycle and is the master clock in mammals. It receives input from the external environment, with the most potent regulator being light received through the retinohypothalamic tract. The suprachiasmatic nucleus coordinates secondary oscillators in other parts of the brain and body (eg, liver, muscle, adipose tissue) via the peripheral nervous system and humoral signals. The release of melatonin is regulated by the suprachiasmatic nucleus and can provide feedback and adjust the timing of suprachiasmatic nucleus activity.

The suprachiasmatic nucleus receives light input from photosensitive retinal ganglion cells that contain melanopsin and sends outputs to other regions of the hypothalamus. Output pathways include neuronal, neuroendocrine, and hormonal mechanisms. Additionally, the suprachiasmatic nucleus' output regulates the timing of rhythmic behaviors via the regulation of peripheral tissue clocks through the secretion of endogenous regulatory factors that are mainly composed of the transcriptional activator proteins clock circadian regulator (CLOCK) and basic helix-loop-helix ARNT-like 1 (BMAL1), along with the repressor proteins period circadian regulator 1 (PER1), 2, (PER2), and 3 (PER3), and cryptochrome circadian regulator 1 (CRY1) and 2 (CRY2).[1] Genes that maintain autoregulatory feedback loops that regulate their own expression are part of the molecular circadian clock (FIGURE 8-1[2]).

An estimated 40% of protein-coding genes display 24-hour rhythmicity in mammals, which suggests that a considerable portion of the transcriptome is controlled by the circadian system.[3]

Circadian rhythms correspond with melatonin levels (measured in saliva, blood, or urine) and core body temperature. Melatonin secretion is highest in the dark (ie, at night), low during times of bright light (ie, during daytime), and varies with age and sex. Bright light directly inhibits melatonin secretion; its suppression is most sensitive to blue light with wavelengths around 460 nm (FIGURE 8-2[4]).

The timing, intensity, duration, and wavelength of light determine the direction and magnitude of light-induced phase shifts of the circadian clocks. Bright light in the evening causes a phase delay (shifts circadian clocks to a later time) and light in the early morning causes a phase advance (shifts circadian clocks to earlier times).

Many physiologic processes follow a circadian rhythm (eg, core body temperature, melatonin and cortisol secretion) and are synchronized or entrained to environmental cues. Cues that synchronize circadian rhythms are called *zeitgebers* ("time givers") and include light (the main zeitgeber), temperature, exercise, food intake and timing, and social activities.

The circadian rhythm temporally organizes our physiologic clocks and health functions and influences sleep-wake propensity, alertness, and performance. These functions are regulated by interactions traditionally described as the endogenous circadian (Process C) and sleep homeostatic (Process S) processes, as well as the influence of external behavioral and environmental factors. In Process S, the longer the waking period, the greater the pressure to sleep. On the other hand, in Process C the circadian alerting signal increases throughout the waking period, has a slight dip in the early to middle afternoon, and peaks in the early evening to maintain wakefulness until bedtime. After reaching its highest point in the evening, the circadian alerting signal decreases, which corresponds

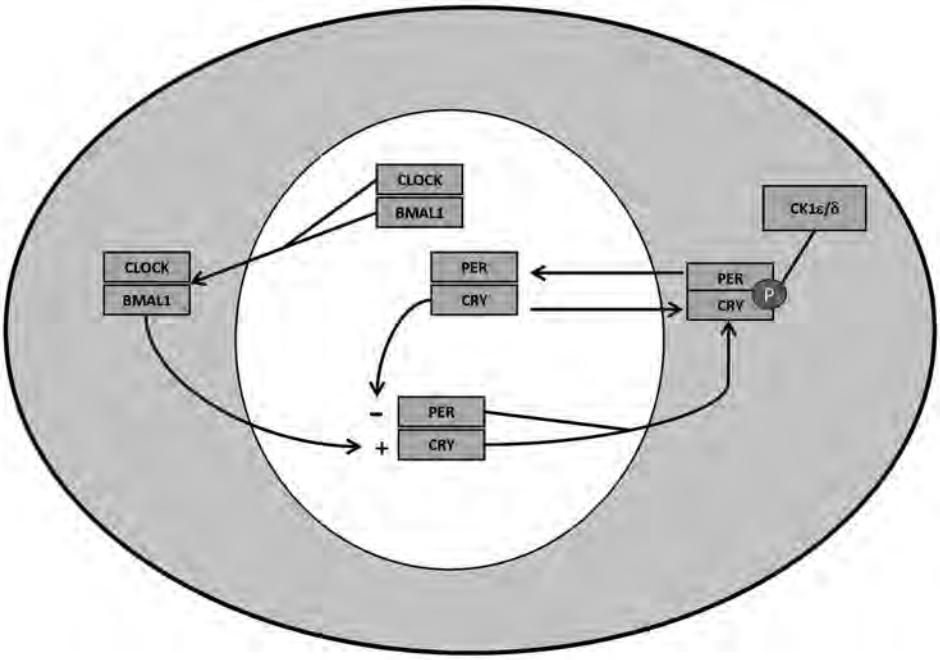

FIGURE 8-1

Core elements of the circadian transcription-translation feedback loop. The gray oval represents the cytoplasm, and the white circle represents the nucleus. *CLOCK* and *BMAL1* are transcribed, translated, and translocated back into the nucleus, where they activate the transcription of *PER* and *CRY*. *PER* and *CRY* are transcribed and translated and dimerize in a rate-limited step mediated by casein kinase 1ε/δ (CK1ε/δ). Eventually, enough PER/CRY dimers build up and are translocated back into the nucleus where they inhibit their own transcription. For most humans, this entire process takes just over 24 hours to complete.

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to the nocturnal secretion of pineal melatonin and a decline in core body temperature. Under typical conditions, low circadian alerting signal and high melatonin help facilitate sleep (FIGURE 8-3[5]).

Cellular and bodily rhythms are highly influenced by physiologic and metabolic stimuli such as diet, exercise, metabolites, gut microbial products, ions, and gaseous molecules (which has been demonstrated in cellular and animal models). Functional circadian oscillators act as a multimodal mechanism that includes individual neurons and fibroblasts of the brain and peripheral organs.[6] Physiologic and metabolic cues, such as proteins and metabolites, prompt a timely response from these oscillators. These cues may have different oscillations in individual tissues, but they can be reprogrammed. The external stimuli that allow for reprogramming include sleep deprivation, aging, the timing of food, and a high-fat diet (FIGURE 8-4[6]).

Dietary content and timing are related to physiologic clock regulation and metabolism. A high-fat diet can disrupt synchrony between central and peripheral clocks. Food intake in the circadian evening or night is associated with a greater amount of body fat, obesity, and decreased effectiveness of weight loss treatments for adults and children.[3] Intestinal microbiota depletion can disrupt peripheral clocks, with subsequent alterations in corticosteroid levels that can contribute to metabolic disorders.[6]

KEY POINTS

- **Circadian rhythms are among the most basic mechanisms that help preserve health. Physiologic clocks regulate body temperature, hormone secretion, appetite, alertness, and most basic body functions.**
- **The suprachiasmatic nucleus is the master clock in mammals and coordinates secondary oscillators in other parts of the brain and body. Melatonin is regulated by the suprachiasmatic nucleus and can provide feedback and adjust the timing of suprachiasmatic nucleus activity.**
- **Genes that maintain autoregulatory feedback loops that regulate their own expression are part of the molecular circadian clock.**
- **Bright light in the evening causes a phase delay (shifts circadian clocks to a later time) and light in the early morning causes a phase advance (shifts circadian clocks to earlier times).**
- **The circadian alerting signal increases across the wake period, has a slight dip in the early to middle afternoon, and peaks in the early evening to maintain wakefulness until bedtime.**

Epigenetic and posttranscriptional regulation also contribute to the molecular clockwork. These regulatory mechanisms affect genes that encode products involved in cellular physiology and metabolism: enzymes, portions of the ubiquitin-proteosome pathway, transporters from the nucleus to the cytoplasm, noncoding RNAs, and remodelers of chromatin.[3] In addition, diet (specifically one that is high in fat) and timing of dietary intake can reprogram the circadian rhythmicity of regions in the brain (eg, the suprachiasmatic nucleus) and of peripheral clocks.

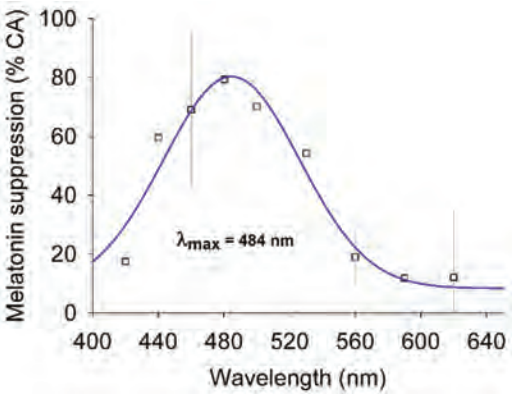

FIGURE 8-2
Action spectrum of acute melatonin suppression by light in humans. Wavelength-dependent melatonin suppression (expressed relative to control-adjusted [CA] melatonin suppression) after 60-minute monochromatic light exposure, at night, at 3.6 × 10^{13} photons/cm^2/s. The fit (*curve*) is a four-parameter Gaussian model (R^2 = 0.94). Maximum suppression was found at 484 nm (λ_{max}).
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The gut microbiomes of mice and humans show diurnal oscillations. The reduction of intestinal microbiota causes circadian disruption in intestinal epithelial cells that leads to altered corticosteroid levels, which in turn contributes to metabolic disorders. In addition, mistimed feeding is associated, at least in part, with dysregulation of gut microbiome products.[6]

Chronotype refers to an individual's preferred timing of wakefulness and activity and may rely on genetic factors. Commonly seen individual variations include morning larks (those who prefer to fall asleep and wake up earlier) and night owls (those who prefer to fall asleep and wake up later). The phenomenon of "social jet lag" is a type of circadian disruption in which a person with delayed chronotype follows their circadian preference for sleep-wake times on days off from work or school, but then needs to awaken early on work or school days. Social jet lag has been associated with depressive symptoms and cardiovascular dysfunction. A delayed chronotype correlates with an increased prevalence of psychological disorders, diabetes, poorer cardiovascular health, and a higher risk of mortality. Chronotype changes with age; older people tend to have dampened oscillations in several circadian traits, such as the release of melatonin and cortisol hormones, which could be linked to some age-related pathologies.[3]

CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Circadian rhythm sleep-wake disorders occur when there is a misalignment between internal rhythms and the timing of social and occupational activities. The term *circadian misalignment* is used to describe a variety of circumstances, such as inappropriate sleep and wake timing, misalignment of sleep and waking with feeding rhythms, or misaligned central and peripheral rhythms. The *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*)[7] defines the minimal criteria to establish the diagnosis, including

(1) a chronic or recurrent pattern of sleep-wake rhythm disruption primarily caused by an alteration in the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the desired or required sleep-wake schedule, (2) a sleep-wake disturbance such as insomnia or excessive sleepiness, and (3) associated distress or impairment. Symptoms should last for at least 3 months (except for jet lag disorder). As defined in the *ICSD-3-TR*, circadian rhythm sleep-wake disorders include the following:

- 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

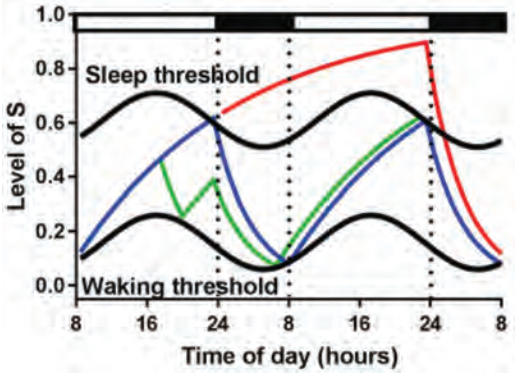

FIGURE 8-3
Simplified representation of the two-process model of sleep regulation. The figure shows a simulation of the homeostatic Process S according to different experimental conditions over 2 days. The normal sleep and wake periods are denoted by black and white bars, respectively. The blue line indicates the baseline condition, with 8 hours of sleep and 16 hours of waking. When the blue line is increasing, the model is awake; when it reaches the upper threshold (the upper sinusoidal black line), the model goes to sleep and the line decreases. This process continues until it reaches the lower threshold and the model awakens again. The green line indicates the effects of a 2-hour nap starting around 6:00 PM followed by a normal night of sleep. The red line indicates sleep deprivation (40 hours of continuous waking by skipping a night) and recovery sleep during the following night. Note that the model assumes that naps and sleep deprivation do not affect circadian regulation throughout the next day.
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Circadian rhythm sleep-wake disorders occur in the setting of comorbid medical, psychiatric, and neurologic disorders.

Overall, little literature exists on the prevalence and racial and ethnic differences of circadian rhythm sleep-wake disorders.

The diagnosis of circadian rhythm sleep-wake disorders is made based on a patient's history and clinical presentation. The use of self-reported sleep diaries, actigraphy (for at least 7 days, and preferably for 14 days), or both can be helpful in the diagnosis of circadian rhythm sleep-wake disorders. Questionnaires to establish chronotype (such as the Horne-Östberg Morningness-Eveningness Questionnaire and the Munich Chronotype Questionnaire) can be helpful but are not required. Some questionnaires are available and scored online (see Useful Websites section). Consumer sleep technologies can provide information about current sleep-wake patterns and feedback on progress as interventions are implemented; while these modalities are easily accessible and hold promise as part of care pathways, they are not currently substitutes for clinically validated devices and assessment tools.

KEY POINTS

- **Emerging studies suggest that multiple metabolic or nutritional cues (eg, time of food intake) are circadian-regulated components, which in turn can act as timing cues to regulate circadian physiology via reciprocal feedback mechanisms.**
- **Chronotype refers to an individual's preferred timing of sleep and wake; misalignment with the environment can cause "social jet lag." Later chronotypes have been associated with worse health outcomes.**

KEY POINTS

- **Circadian misalignment increases cardiovascular disease risk and is associated with an increased risk of cancer, autoimmune disease, and psychiatric disorders.**
- **Shift work disorder is seen when work occurs, at least in part, during the usual main sleep episode. Typically, total sleep is shortened by 1 to 4 hours and sleep quality is perceived as unsatisfactory during the available sleep time.**
- **Evidence shows that circadian disruption has a negative effect on neurologic disorders such as cerebrovascular disease, epilepsy, pain, migraine, multiple sclerosis, neurodegenerative disorders, and neurodevelopmental disorders.**

Although not required, another factor to consider in the evaluation of possible circadian rhythm sleep-wake disorders is the measurement of biomarkers such as dim light melatonin onset. Dim light melatonin onset assessment is often used in research protocols and requires serial plasma sampling in the evening in dim light to measure melatonin level, which is not feasible in standard clinical practice. The cost and burden of collecting dim light melatonin onset data limit its use in clinical practice. Some peripheral blood assays combined with computational tools can provide an accurate measurement from a single sample and may prove to be useful in the future.

Shift work disorder and jet lag disorder are extrinsic circadian rhythm sleep-wake disorders that are common in our society but are not often seen in the clinic. Shift work disorder is seen when work occurs, at least in part, during the usual main sleep episode. Typically, total sleep is shortened by 1 to 4 hours and perceived sleep quality is unsatisfactory during the available sleep time. The resultant reduced alertness or increased fatigue during wakefulness can cause decreased performance, irritability, poor concentration, headaches, impaired social functioning, and safety issues. Estimates show that 20% of the workforce in industrialized countries is required to do some shift work. Each person's ability to adapt to work times depends on their individual circadian preference (CASE 8-1).

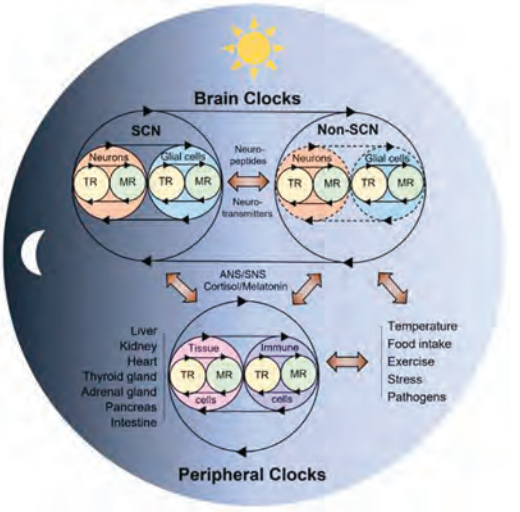

FIGURE 8-4

Coupled-tissue oscillators. The figure shows reciprocal crosstalk between the brain and peripheral physiologic clocks. The coupled transcriptional-rhythm (TR) and metabolic-rhythm (MR) oscillators are thought to be present in all body cells. Neurons and glial cells (eg, astrocytes, microglia) interact to form the suprachiasmatic nucleus (SCN) central clock and non-SCN clocks in the brain. These autonomous brain clocks communicate with each other via neurotransmitters or neuropeptides, and with multiple peripheral tissue clocks via systemic innervations (autonomic nervous system [ANS], sympathetic nervous system [SNS]) or hormonal signals (eg, cortisol, melatonin) in response to light-dark cycles. On the other hand, peripheral organs possess tissue autonomous clocks that can respond to nonphotic physiologic and environmental cues (eg, temperature, food intake, exercise, stress) and provide feedback that influences the brain clocks via immune, metabolic, and endocrine signals.

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Jet lag disorder occurs due to travel across at least two time zones, with subsequent trouble adjusting to the new schedule. Internal clocks usually adjust by 1 hour (one time zone) per day. Adjusting to eastward travel is usually more difficult than adjusting to westward travel, although individual variations occur in the ability to adjust to time zone changes. Older adults may have more severe jet lag and may need a longer time to recover. Individuals affected by jet lag may have impaired daytime function, insomnia, sleepiness, malaise, tiredness, a sense of disorientation, gastrointestinal distress, or worsened menstrual symptoms.

Delayed sleep-wake phase disorder occurs when sleep-wake times are delayed relative to conventional norms or desired times (ie, biological preference to go to bed late and wake up late). Delayed sleep-wake phase disorder is more common in adolescents and young adults (CASE 8-2). A positive family history has been described in about 40% of cases. Several studies demonstrate that an evening chronotype is associated with an increased risk for physical and mental health concerns, such as higher rates of depression, suicidality, impairment of academic functioning, substance use, and decreased health-related quality of life.

Advanced sleep-wake phase disorder is seen when biologically preferred sleep-wake times occur earlier than conventional times. Advanced sleep-wake phase disorder is more common in older patients. Cases of familial advanced sleep-wake phase disorder have been described.

Irregular sleep-wake rhythm disorder is seen in people who lack clearly defined sleep-wake periods, with three discrete sleep episodes at variable times over 24 hours. Poor sleep hygiene, lack of exposure to photic zeitgebers (ie, light exposure), nonphotic zeitgebers (eg, exercise, timing of meals, and social interactions), or both may predispose someone to or precipitate irregular sleep-wake rhythm disorder (CASE 8-3). Irregular sleep-wake rhythm disorder is commonly seen in children with developmental disorders (such as Angelman syndrome, Williams syndrome, and Smith-Magenis syndrome) or adults with

CASE 8-1

A 38-year-old man presented to the clinic with worsened job performance, irritability, and cognitive decline over the past several months. These symptoms began after he started working the night shift. He struggled to stay awake at work and in response increased his caffeine intake, but this worsened his anxiety as well. He had obstructive sleep apnea, and his daytime sleepiness and snoring initially resolved when he started positive airway pressure treatment. A review of the positive airway pressure device-generated data revealed the typical "flip-flop" of his sleep schedule during days on and off from work. Based on these findings and his reported symptoms, he was diagnosed with shift work sleep disorder.

He was recommended to follow a regular schedule even on days off from work and optimize sleep during sleep times with measures such as a quiet, cold, dark room, avoidance of light exposure before sleep, and exposure to light and exercise upon waking. He was prescribed modafinil 200 mg to be taken before his work shift. His family was engaged to help him adhere to his schedule, and his presenting symptoms had resolved at his 2-month follow-up, with only occasional modafinil use.

COMMENT

This case exemplifies a common situation when a person engages in shift work, followed by usual recommendations provided to address the condition. A combination of behavioral and pharmacologic interventions may be required.

neurodegenerative disorders (such as dementia, Alzheimer disease, Parkinson disease, and Huntington disease). Worsening late-day confusion in patients with cognitive impairment or dementia may represent a clinical subtype of irregular sleep-wake rhythm disorder.

Non-24-hour sleep-wake rhythm disorder (previously referred to as *free-running disorder*) is seen in over 50% of individuals who are totally blind. If the inner retina photosensitive ganglion cell layer and the retinohypothalamic pathway are retained, the circadian rhythms may be preserved. Nonphotic zeitgebers may help some individuals who are blind retain circadian rhythms. Sleep-related concerns are noted in 50% to 80% of people who are blind. People with non-24-hour sleep-wake rhythm disorder experience alternating symptoms of insomnia or daytime sleepiness due to misalignment of their endogenous period, which is usually slightly longer than 24 hours. Sighted people with non-24-hour sleep-wake rhythm disorder tend to present with an endogenous period that is often 25 hours or longer. Scheduled melatonin administration may be helpful for people with no light perception. The US Food and Drug Administration (FDA) has approved tasimelteon for the treatment of non-24-hour sleep-wake disorder, to be taken 1 hour before bedtime. For sighted people, timed light exposure may be beneficial as well.

Circadian sleep-wake disorder not otherwise specified is given as a diagnosis for people who meet the general diagnostic criteria for a circadian sleep-wake disorder but do not meet the criteria for a specific type. This diagnosis is intended mainly for people with an underlying medical, neurologic, or psychiatric disorder as a precipitating factor for their circadian disruption. FIGURE 8-7[2] shows example logs for circadian rhythm sleep-wake disorders.

CASE 8-2

A 26-year-old woman presented to the clinic for evaluation of severe insomnia. She had no significant past medical history, but she felt that her difficulty falling asleep had worsened during high school when she had problems falling asleep before 1 AM or 2 AM and frequently missed morning classes. In college, she did not have sleep problems or insomnia since she was able to take most classes in the afternoon, and mainly slept from 4 AM until 11 AM or 12 PM. Her new job required her to start at 9 AM. She tried to go to bed around 10 PM so she could get enough sleep before waking at 6:30 AM, but found that she remained in bed awake for 2 to 3 hours before falling asleep.

She was provided with educational and behavioral counseling to follow good sleep hygiene, avoid light before bedtime, and keep a strict schedule for her sleep times that was gradually shifted to earlier times. She was encouraged to be exposed to bright light, eat breakfast, and exercise in the mornings.

COMMENT

Sleep-onset insomnia is common in patients with delayed sleep-wake phase syndrome. The patient in this case reported having a delayed chronotype, which did not present issues during college as she could align her school and social schedules with her preferred sleep-wake schedule.

TREATMENT OF CIRCADIAN RHTHYM SLEEP-WAKE DISORDERS

No universal treatment exists for circadian rhythm sleep-wake disorders; treatment protocols are individualized. Educational and behavioral counseling on good sleep hygiene is a key treatment component. Behavioral modifications include sleep scheduling (implementation of prescribed sleep and wake times), exposure and avoidance of bright light at specified times, and timed administration of melatonin or alerting agents. Chronotherapy guides patients to entrain their circadian rhythms to achieve desired sleep-wake times; evidence for the use of this therapy is limited to case studies. In general, prescribed sleep times are set and shifted gradually. Dim light exposure is prescribed for 2 hours before bedtime to facilitate endogenous melatonin release, and artificial bright light or sunlight exposure is prescribed for 60 minutes following wake time. After reaching the desired sleep-wake schedule, strict adherence to the prescribed sleep hours is recommended, along with a maintenance dose of 30 minutes of bright light after wake-up time to maintain entrainment. Minimal side effects are associated with phototherapy, although hypomania has been described as a potential adverse effect of light therapy.[8]

Environmental changes can help maximize circadian alignment and improve sleep hygiene around the designated sleep-wake times. A cool, dark sleeping environment with minimal disturbances, noises, or interruptions can help establish a sleep-conducive routine. An eye mask, blackout curtains, earplugs, white noise, and silenced phone notifications or alarms can all help create a dark, quiet sleep environment. Scheduled naps can be done if "catch-up" sleep is needed, although these should not be too close to bedtime. Regular exercise, a balanced diet, and eating one's last meal approximately 3 hours before bedtime are recommended to establish a healthy sleep routine.

Endogenous melatonin affects circadian rhythms and sleep, along with temperature regulation, reproductive cycles, mood, tumor growth, and aging. Exogenous melatonin also has a hypnotic effect in a dose-dependent manner, particularly when administered at a time distinct from endogenous melatonin production. Low doses of melatonin (<0.5 mg) in combination with dim light and recumbency induce sleepiness or sleep. At low melatonin doses (0.5 mg to 5 mg) side effects can include headache, nausea, dizziness, and drowsiness; while side effects tend to be mild with low medication doses, these effects should be assessed to ensure safety with use. Safety data for long-term melatonin use are lacking.[8] In the United States, melatonin is considered a dietary supplement and is not regulated, with wide variations in the content of the active drug across different preparations. One study found that melatonin content ranged from −83% to +478% of the labeled content, and serotonin was identified as well in some of those preparations.[9]

Hypnotics may be used to treat insomnia associated with jet lag, but there is little evidence of their efficacy and potential benefits must be weighed against medication side effects. Cognitive behavioral therapy could be useful as well.

When possible, a worker's shift schedule should be tailored to their individual chronotype. Shift workers with an inconsistently alternating work schedule may attempt to establish a "compromise phase" that maximizes the number of overlapping sleep hours on a daily basis. A scheduled nap before the shift or caffeine intake may improve alertness while at work.

The FDA has approved the wakefulness-promoting medications modafinil and armodafinil for the treatment of shift work disorder. These agents should be taken before or at the start of the shift to boost alertness. If needed, melatonin or hypnotics may be used before the scheduled sleep period. The timing of alerting or hypnotic medication should be carefully planned to avoid adverse outcomes such as motor vehicle accidents due to drowsiness.

There is growing interest in further evaluating the efficacy of a multimodal approach to therapeutically target peripheral and central physiologic clocks. Some strategies include time-restricted feeding, dynamic circadian smart environments (such as smart lighting and temperature in homes and workplaces), and manipulation of the type and timing of noises.

CASE 8-3

A 58-year-old woman with frequent severe headaches, depression, and chronic back pain (for which she took opioids) was referred for evaluation of possible sleep apnea. She experienced choking, gasping, and snoring while sleeping, and her bed partner reported witnessing apneas while the patient was asleep. She slept in bouts of 3 to 4 hours at a time, in either a chair or her bed. A baseline polysomnogram showed obstructive sleep apnea and she began positive airway pressure treatment, which she used every time she slept. The positive airway pressure device-generated data were consistent with her history of an irregular sleep cycle (FIGURE 8-5).

In addition to the positive airway pressure treatment for her obstructive sleep apnea, she was prescribed a strict sleep-wake schedule that her family helped enforce by keeping her active and engaged during the day and maintaining sleep hygiene measures (eg, timing of meals and medications, light exposure). The patient reported more regular sleep-wake hours over time with a significant improvement in quality of life, mental health, pain, and headache frequency (FIGURE 8-6). A year later she maintained better control of her pain and quality of life and was able to decrease her medications, with her opioid dose being reduced to one-third of the original.

COMMENT

This case illustrates a patient with an irregular sleep-wake rhythm disorder with sleep occurring at variable times over 24 hours. Patients often require supportive behavioral interventions from family members. This case also illustrates how management of an underlying sleep disorder may improve comorbidities.

Chronotherapy

Chronotherapy is the concept of timing therapy of neurologic and systemic disorders to optimize efficacy and minimize side effects. Chronotherapy may prevent up- or down-regulation of receptors during periods of lesser need, which allows for optimal efficacy during periods of disease exacerbation. There are three main approaches: (1) training the physiologic clock, which involves actions to create or maintain an optimal circadian rhythm; (2) drugging the physiologic clock, which involves using drugs that manipulate the circadian clock genes to affect circadian rhythms; and (3) clocking the drugs, which involves optimizing the timing of drug administration to minimize drug side effects, increase efficacy, or both. Of note, approximately 119 of the World Health Organization's

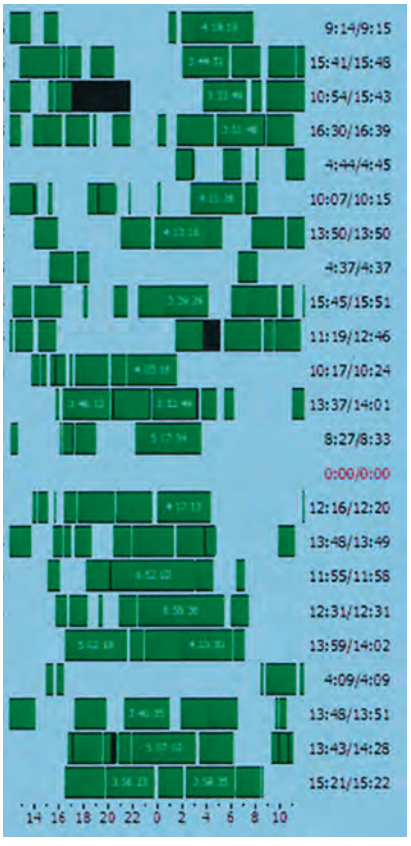

FIGURE 8-5
Positive airway pressure device-generated data for the patient in CASE 8-3 with a history of irregular sleep-wake rhythm disorder. Each row represents 1 day, where the *green bars* indicate the periods that the patient is using the device (with total daily use times listed on the right). The usage pattern becomes more regular as the patient acclimates to the recommended treatment schedule.

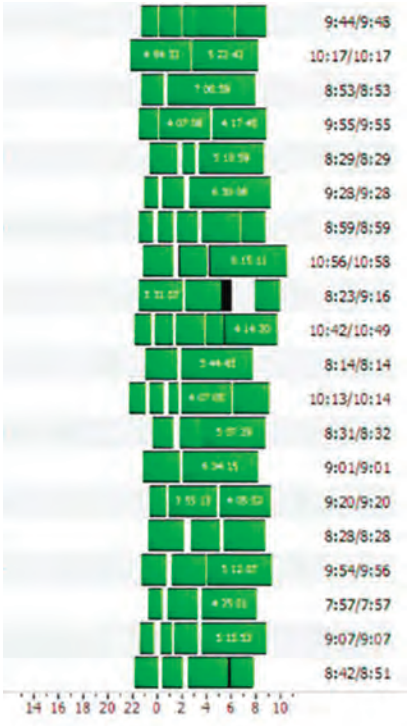

FIGURE 8-6
Positive airway pressure device-generated data for the patient in CASE 8-3, following initial treatment. Each row represents 1 day, where the *green bars* indicate the periods that the patient is using the device (with total daily use times listed on the right). The patient has established a usage routine, as shown by the regularity of her sleep (*green*) and wake (*no data*) timings.

250 essential medicines exert their effects on genes that undergo circadian oscillation.

Circadian changes in blood-brain barrier permeability could be leveraged to improve disease therapy. A cohort of people with epilepsy, treated with phenytoin and carbamazepine at 8 PM, when P-glycoprotein–mediated efflux is low, experienced more effectively decreased seizure burden and side effects compared to the typical twice daily administration.[10]

The application of circadian science is also pertinent in the treatment of cancer. Clinical trials have confirmed that the optimal timing of treatment with chemotherapeutics or immunotherapies could decrease drug toxicity and increase efficacy. Chronoradiotherapy seems to minimize treatment-related symptoms rather than influence tumor progression or patient survival.[11]

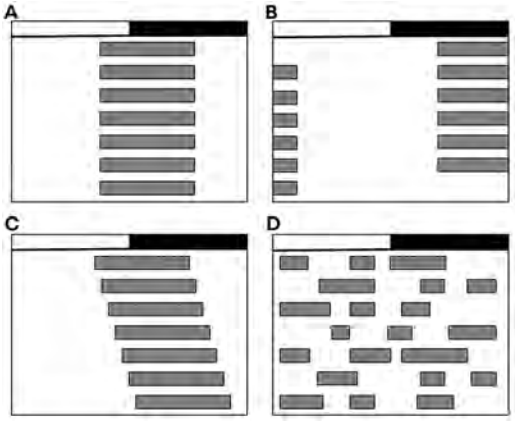

FIGURE 8-7

Example sleep logs demonstrating typical sleep-wake patterns in advanced sleep-wake phase disorder (*A*), delayed sleep-wake disorder (*B*), non-24-hour sleep-wake rhythm disorder (*C*), and irregular sleep-wake rhythm disorder (*D*). Each row indicates 24 hours, with the white and black boxes indicating daytime and nighttime, respectively. The gray shaded boxes indicate the timing of sleep bouts in relation to the light-dark cycle.

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CLINICAL CORRELATIONS OF CIRCADIAN DISRUPTION

The effects of circadian dysregulation have wide implications at the societal and personal levels. Many aspects of these implications have recently gained attention, but many more areas have not yet been fully explored.

Public Health Implications

Circadian disruption can result in significant mental and physical health consequences. Exposure to artificial light at night results in a disruption of the circadian system and is associated with negative health consequences.[12] A large portion of the population is at risk for circadian disruption due to artificial light exposure. In the United States, an estimated 16% of the population works a nondaytime shift; 70% of the population works indoors, may experience social jet lag, or both; 99% of the population is affected by light pollution; and a growing percentage of the population is aging.[13]

Daylight Saving Time, in which external clocks shift forward an hour, causes circadian disruption via misalignment of environmental cues that regulate circadian entrainment (namely, morning light) and external clock time. Adoption of permanent Daylight Saving Time would worsen circadian disruption for most residents of the United States and further fuel health disparities, whereas permanent Standard Time would best sync environmental cues with the internal clock.[14,15] This topic is discussed in more detail in the article "Implications of Sleep Health Policy: Daylight Saving and School Start Times," by

Karin G. Johnson, MD, FAAN, FAASM, and Beth A. Malow, MD, MS, FAAN,[16] in this issue of *Continuum*.

Individual Health Implications

The American Heart Association integrated sleep into the Life's Essential 8 campaign, which includes recommendations to get healthy sleep.[17] The relationship between reduced sleep duration and insomnia with increased cardiovascular disease risk is well established. Inconsistent sleep timing, delayed chronotype, and social jet lag are also associated with increased cardiovascular disease risk.

For example, blood pressure typically exhibits a cardioprotective nocturnal decrease, or "dipping," that is regulated by increased parasympathetic tone. Circadian misalignment alters this cardioprotective effect.[13] Circadian influence is seen in the higher likelihood of myocardial infarctions in the morning hours[18]; the same timing association is noted for ventricular arrhythmias and stroke. Circadian misalignment increases the risk of cardiovascular disease, hypertension, and elevated levels of systemic inflammatory markers such as C-reactive protein.[19]

Timing of food consumption is a critical factor for metabolic health, independent of total caloric intake and macronutrient quality. Chronic circadian rhythm disruption increases the risk of metabolic diseases; time-restricted feeding, in which nutrient intake is limited to a specific window of time every day, sustains robust diurnal rhythms and can alleviate metabolic diseases.[20]

Epidemiologic and clinical studies show that circadian disruption causes impaired glucose tolerance. Disrupted meal timing leads to impaired glucose tolerance and weight gain. Time-restricted feeding seems to improve metabolic disorders related to diet-induced obesity and reproduces the metabolic profile found in caloric restriction, which may promote healthy aging.[21]

Individuals with a delayed chronotype (greater circadian misalignment) are more likely to be overweight and have type 2 diabetes. People with type 2 diabetes and a delayed chronotype have poorer glycemic control compared with people with type 2 diabetes who have less circadian misalignment. People with disrupted circadian rhythms have a higher incidence of obesity.[13] Disruption of the circadian clock due to shift work, sleep restriction, or *CLOCK* gene knockout in animal models is associated with osteoporosis or other abnormal bone metabolism.[22] In shift workers, misalignment between environmental cues and the suprachiasmatic nucleus also appears to increase the risk of allergic disorders and the risk of pulmonary diseases such as asthma.[13]

The association between cancer and circadian rhythms is becoming more apparent. Molecular mechanisms regulate steps within the cell cycle that control cell division. For example, mitosis occurs at specific times of the day in mammals. Circadian clocks also control DNA repair checkpoints, alterations in the morphology of mitochondria, and the process of nucleotide excision repair. Mutations in circadian clock genes may affect the strict cell cycle regulation seen in noncancer states and allow cancer cells to proliferate more rapidly.[11]

The Nurses' Health Study showed an increased risk of breast cancer in association with night shift work, in addition to evidence of an increased risk of colorectal disease.[23] More recent studies have shown an increased risk of

KEY POINTS

- Delayed sleep-wake phase disorder occurs when sleep-wake times are delayed relative to conventional norms or desired times (ie, biological preference to go to bed late and wake up late) and is more common in adolescents and young adults.
- Irregular sleep-wake rhythm disorder is seen in people who lack clearly defined sleep-wake periods, with three discrete sleep episodes at variable times over 24 hours.
- People with non-24-hour sleep-wake rhythm disorder experience alternating symptoms of insomnia or daytime sleepiness due to misalignment of their endogenous period, which is usually slightly longer than 24 hours.
- In patients with circadian rhythm sleep-wake disorders, dim light exposure is prescribed for 2 hours before bedtime to facilitate endogenous melatonin release, and artificial bright light or sunlight exposure is prescribed for 60 minutes following wake-up time.
- Chronotherapy is the concept of timing therapy for neurologic and systemic disorders to optimize efficacy and minimize treatment side effects.

melanoma with exposure to light at night.[21] A population-based case-control study showed that circadian disruption of eating patterns was associated with an increased risk of breast and prostate cancers.[6]

The immune system also shows strong circadian rhythmicity. For example, cortisol levels peak in the early morning and reach their lowest levels during the second half of the night. Other inflammatory markers such as blood undifferentiated T lymphocytes and natural killer cells are at their highest during the sleep period; proinflammatory cytokines (such as interleukin [IL]-1β and tumor necrosis factor-α [TNF-α]) peak during the resting period, and anti-inflammatory cytokines (such as IL-4 and IL-10) peak during the active period. These variations could alter the efficacy of immunotherapy treatments.[18]

A bidirectional relationship exists between sleep and circadian disturbances and autoimmune disease. It is thought that dysregulated homeostatic cytokine expression in autoimmune disease contributes in part to sleep disturbances in individuals with autoimmune disorders. Sleep loss in turn enhances proinflammatory cytokines that could exacerbate sleep disturbances and autoimmune disease.

Melatonin has anti-inflammatory and antioxidant properties and may attenuate the expression of IL-1β, TNF-α, IL-6, and IFN-γ. The anti-inflammatory properties of melatonin are due in part to the inhibition of necrosis factor-κB.

Circadian disruption has also been associated with multiple psychiatric disorders, including bipolar disorder, depression, anxiety, seasonal affective disorder, schizophrenia, attention deficit hyperactivity disorder, and autism. It has also been shown to affect mental performance and increase negative emotions. The sleep midpoint is the time point midway between bedtime and waking up; the later the sleep midpoint, the more likely a person will have a later chronotype. A recent study of thousands of patients in several large cohorts identified that an earlier sleep midpoint was associated with a 23% lower risk of depression. The relationship between circadian disruption and mood disorders has been established for a long time, as clearly featured in seasonal affective disorder and the effects of bright light as a therapeutic option.[13]

Circadian disruption increases the risk for neurologic disorders across the lifespan.[24] Increasing evidence suggests that circadian disruption can contribute to the risk of cerebrovascular disease, epilepsy, pain, migraine, multiple sclerosis, neurodegenerative disorders, and neurodevelopmental disorders. Individuals with disruption of sleep and circadian rhythmicity are more likely to have problems with cognitive function, such as greater mood instability and slower reaction times.[9] Poor sleep and circadian disruption are common in neurodevelopmental disorders (in particular, in Angelman, Williams, Prader-Willi, fragile X, and Smith-Magenis syndromes), including autism spectrum disorders. A hypothesis is that individuals with autism spectrum disorders have a dysfunction of melatonin synthesis, and melatonin should be offered if initial behavioral interventions are not sufficiently effective.[25]

Disrupted circadian rhythms are evident in patients with neurodegenerative disorders, and a bidirectional relationship has been noted in conditions such as traumatic brain injury, Alzheimer disease, Parkinson disease, and Huntington disease. Preclinical and clinical studies have correlated circadian disruption with the accumulation of neurotoxin proteins and neurodegeneration itself.[20] Physiologic clocks control astrocyte and microglia function and contribute to the control of sleep and the rhythmic clearance of neurotoxin proteins through the

glymphatic system or sleep-driven changes in CSF flow. The circadian control of oxidative or proteotoxic stress may play a part in neurodegeneration.[21]

The permeability of the blood-brain barrier is dynamically controlled by circadian rhythms and sleep, promoting the clearance of metabolites as well as endocytosis and the entry of hormones.[10]

Sleep and circadian disruption are common in Alzheimer disease, affecting up to 40% of patients with mild to moderate dementia. Sleep deprivation promotes the deposition of amyloid-β proteins into insoluble amyloid plaques. Cognitively intact individuals who have evidence of amyloid plaques have worse quality of sleep and sleep efficiency and more overnight awakenings compared with healthy controls.[24] Circadian disruption occurs at multiple levels in patients with Alzheimer disease; there is loss of suprachiasmatic nucleus neurons, impaired function of light input pathways, decreased exposure to light, and reduced structured activity, all of which collectively contribute to low amplitude and misalignment of the circadian rhythm, correlating with the degree of neurologic impairment. Light therapy, behavioral modifications, and melatonin therapy are increasingly used for patients with Alzheimer disease and have led to improvements in Mini Mental Examination State scores in patients with mild Alzheimer disease.[13]

The impact of circadian dysregulation on sleep disturbances in Parkinson disease is not fully understood. Impaired sleep and alertness are among the most common nonmotor manifestations of Parkinson disease and affect up to 90% of these patients. Both motor and nonmotor manifestations of Parkinson disease demonstrate strong diurnal oscillations. The circadian pattern of motor symptoms in Parkinson disease is characterized by the worsening of motor functioning in the afternoon and evening, a phenomenon that occurs in patients with and without motor fluctuations. Autonomic functions can also be altered, including a reversal of blood pressure rhythms (ie, increasing during the night rather than decreasing).[24] Bright light therapy has been shown to improve mood, increase objective levels of physical activity, and enhance sleep in patients with Parkinson disease.[13]

Approximately 55% of all ischemic strokes, 34% of all hemorrhagic strokes, and 50% of all transient ischemic attacks occur between 6:00 AM and 12:00 PM.[24]

It has long been known that seizures oscillate regularly over days, months, and years. There is a nocturnal peak for interictal epileptiform discharges. *CLOCK* gene expression may be reduced within the epileptogenic focus in patients with refractory epilepsy.[26] The detection and tracking of variation in seizure cycles should be incorporated into epilepsy management practices.

Little is known about circadian rhythms in multiple sclerosis. There are reports of a higher prevalence of self-referred circadian rhythm sleep disorders in a sample of patients with relapsing-remitting multiple sclerosis, and a study demonstrated a peak in motor activity around 5:00 AM that was higher than that in control groups without multiple sclerosis.[27]

The pain system exhibits circadian rhythms in function and pain responsiveness varies throughout the day, with the highest pain sensitivity at the end of the active phase and during the night, but with dramatic variations in response to disease. The opioid, immune, and endocrine systems may influence the circadian rhythms of pain. Night shift work correlates with reduced pain thresholds and increased risk for lower back pain. Multiple chronic and maladaptive pain conditions are associated with altered circadian rhythms in

KEY POINTS

- **Circadian rhythm sleep-wake disorders are clinical diagnoses that manifest due to misalignment between internal rhythms and the timing of external activities.**
- **Circadian disruption increases the risk for neurologic disorders across the lifespan.**
- **Light exposure before bedtime delays the internal clock, whereas light exposure in the morning advances circadian timing. Educational and behavioral counseling on good sleep hygiene, sleep scheduling, and light exposure are parts of circadian rhythm sleep-wake disorder treatment.**

KEY POINTS

- Many chronic pain conditions are associated with disrupted circadian rhythm and sleep-wake rhythms, establishing a maladaptive feedback loop.
- Health disparities in circadian misalignment are common, with Black and Hispanic populations being twice as likely to work night shifts compared to White populations.

pain thresholds. Pain peaks in the early morning in patients with fibromyalgia and rheumatoid arthritis, in late morning or early afternoon in patients with cancer, and at night in patients with diabetic neuropathy and postherpetic neuralgia.[28] The peak onset of migraine attacks occurs during morning hours.[29] In turn, many chronic pain conditions are associated with disrupted circadian rhythm and sleep-wake rhythms, establishing a maladaptive feedback loop. Further research is needed to understand the relationship between chronotype and pain threshold rhythms to optimally apply chronotherapy.[28]

HEALTH DISPARITIES AND CIRCADIAN RHYTHM DISORDERS

A longitudinal study of White, Chinese, Black, and Hispanic American adults found that sleep irregularity was greater among Black participants compared to all other groups; greater sleep irregularity was also correlated with greater risks of obesity and hypertension, and increased depression severity and perceived stress.[30] Black individuals in the United States may be at increased risk of circadian rhythm disorders due to occupational, environmental, and health care access–related factors.[31] Risk factors for circadian disruption such as night shift work, exposure to light or noise pollution, and residential segregation (eg, homes closer to highways or factories, overcrowding) and its consequences, including obesity, stress, and sleep deprivation, disproportionately affect Black individuals and may exacerbate existing racial health disparities.

Black and Hispanic adults are twice as likely to work night shifts compared to White adults. In 2017, the International Agency for Research on Cancer identified rotating shift work, in association with circadian disruption, as a probable human carcinogen, and placed it in the same risk category as ultraviolet radiation, benzo(a)pyrene, and acrylamide.[31]

A longitudinal study found that female nurses who worked night shifts for over 30 years displayed a 36% increased relative risk of breast cancer. Men with a rotating shift schedule have a 20% higher risk of developing prostate cancer compared with those who have a fixed night shift schedule.[31]

A study using data from the Multi-Ethnic Study of Atherosclerosis (MESA) examined circadian misalignment (depicted as regularity of sleep-wake schedules) and cardiometabolic risk. The study used the sleep regularity index, which is defined as the percentage probability of a person being asleep or awake at any two time points 24 hours apart. Sleep regularity index scores were lower among Black participants compared with all other groups ($P < 10^{-5}$), and lower among Hispanic participants compared with White participants ($P < 10^{-5}$).[30] Sleep irregularity is correlated with increased perceived stress and depression, a higher 10-year risk of cardiovascular disease, greater risk for obesity, hypertension, diabetes, and higher fasting glucose hemoglobin A_{1C} levels.

CONCLUSION

Circadian rhythm dysfunction is ubiquitous in our society. Robust evidence shows that the misalignment of circadian clocks has deleterious consequences for our health.

The treatment of circadian rhythm sleep-wake disorders may facilitate the management of comorbidities and improve patient outcomes. Behavioral interventions, such as the maintenance of a regular schedule that includes meal

timings, physical activity, and exposure to light or darkness, should be discussed. Melatonin may be considered in the appropriate clinical context.

Further research on circadian biology and clinical applications will require an interdisciplinary approach that encompasses multiple aspects of health. Advanced understanding of the role of circadian rhythms across diverse disease entities, inclusive of chronotherapeutic interventions, could have a tremendous potential to improve human health.

USEFUL WEBSITES

AMERICAN ACADEMY OF SLEEP MEDICINE (AASM) SLEEP EDUCATION
The AASM Sleep Education website provides information on multiple sleep topics, with different sections for patients, caregivers, and educators, available in several languages.

sleepeducation.org/sleep-disorders/#_circadian-rhythm

AUTOMATED MORNINGNESS-EVENINGNESS QUESTIONNAIRE (AutoMEQ)
An automated version of the morningness-eveningness questionnaire that provides scoring of individual circadian rhythm type and feedback.

chronotype-self-test.info

SOCIETY FOR RESEARCH ON BIOLOGICAL RHYTHMS
Information on biological rhythms, including education and advocacy sections.

srbr.org/about-chronobiology/what-are-biological-rhythms

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Insomnia

By Scott Kutscher, MD; Christine Juang, PhD, DBSM

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **This article provides an overview of the current definitions, diagnostic tools, and overall management of insomnia.**

LATEST DEVELOPMENTS: **The treatment of insomnia has shifted over time, with a growing emphasis on nonpharmacologic therapies as a first-line intervention and the leveraging of technology to aid in the dissemination of these therapies. With this evolution, the definition of insomnia has changed to reflect a common treatment pathway. As pharmacologic treatment options have increased, so has concern about the dangerous short-term and long-term adverse effects of these treatment options.**

ESSENTIAL POINTS: **Insomnia is a common disorder, frequently overlapping with other neurologic and psychiatric disorders, which can cause significant distress and disruption to patients' lives. Nonpharmacologic therapies are highly effective and are now considered first-line treatments. Although efficacy is variable, numerous pharmacologic interventions are available, and many options come with considerable concern about adverse effects, particularly in populations over 65 years old.**

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RELATIONSHIP DISCLOSURE:
Dr Kutscher has received personal compensation in the range of $5000 to $9999 for serving as a consultant for Jazz Pharmaceuticals, Inc. Dr Juang reports no disclosure.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Kutscher and Dr Juang discuss the unlabeled/investigational use of diphenhydramine, doxepin, gabapentin, hydroxyzine, mirtazapine, quetiapine, and trazodone for the treatment of insomnia.

INTRODUCTION

Insomnia is the most common sleep disorder. Although prevalence estimates vary by the definition and assessment of insomnia, approximately one-third of the general population experience symptoms of insomnia, and 6% have an insomnia disorder.[1] Insomnia is a public health concern with high societal costs caused by an increase in the use of health services and products, work-related impairments, and poor health-related quality of life.[2] This article describes the definitions and pathophysiology of insomnia, recommendations for the clinical management of insomnia, and opportunities and challenges that come with technologic advances.

CURRENT AND HISTORICAL DEFINITIONS

Three major classification systems describe insomnia disorder: the *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*), the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, and the *International Classification of Diseases, Eleventh Revision*. Although classifications and subclassifications of insomnia disorder have changed over time and varied between classification systems, three core characteristics have emerged at the heart of an insomnia diagnosis: (1) difficulty sleeping, (2) little to no sleep despite adequate opportunity for sleep, and (3) associated daytime dysfunction. All three criteria must be present for a diagnosis of insomnia, although objective

KEY POINT

- A diagnosis of chronic insomnia is defined as difficulty falling asleep or maintaining sleep three or more times per week in conjunction with at least 3 months of associated daytime dysfunction.

verification of subjective symptoms is not required, and a diagnosis can be made by history alone with the *ICSD-3-TR*. This article outlines the diagnostic criteria for insomnia using the *ICSD-3-TR*.

Insomnia Typing and Subtyping

The classification of insomnia has changed significantly over time. Initially, insomnia was considered a symptom of other disorders such as depression or anxiety. Once insomnia was recognized as a unique disorder, the *International Classification of Sleep Disorders, Second Edition* subdivided insomnia conditions into 11 distinct diagnoses reflective of different conditions, behaviors, or states. However, this rubric largely ignored the fact that insomnia treatment was similar regardless of etiology and failed to recognize the challenges in differentiating cause and effect.[3] Hence, the new insomnia subtype definitions focus only on the duration of the symptoms: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder.

Diagnostic Criteria

Insomnia disorder is present when there is difficulty initiating or maintaining sleep, or waking up earlier than desired, despite an adequate opportunity for sleep. The identified disturbance results in daytime dysfunction that cannot be explained better by another sleep disorder or cannot be solely explained by another disorder (eg, a patient who cannot sleep when they have back pain, but only when they have back pain). In most cases, a clinically significant threshold for diagnosis is 30 minutes: a sleep-onset latency of more than 30 minutes, prolonged awakening of at least 30 minutes, or terminal awakening 30 minutes before desired wake-up time. Shorter time thresholds may be considered clinically significant in younger adults. The spectrum of daytime dysfunction is broad and includes fatigue, decreased energy or motivation, behavioral problems or mood disturbances, difficulty with attention and concentration, impairment of social interaction or work performance, excessive daytime sleepiness, and dissatisfaction with sleep quality.

A person is diagnosed with chronic insomnia when these symptoms are present at least three times per week for at least 3 months. If the symptoms have been present for less than 3 months, a diagnosis of short-term insomnia disorder is appropriate. Other insomnia disorder is a rarely used diagnosis for when either the nature or timeline of symptoms is unclear or when symptoms do not meet the criteria for chronic or short-term insomnia disorder.

Pediatric Populations

The diagnostic criteria described above apply to adult and pediatric patient populations, although a diagnosis should not be made before age 6 months, the developmental age when sleep is fully consolidated. Some features of insomnia, such as inappropriate sleep-onset associations, can be more prominent in children. An example of inappropriate sleep-onset association is a child who can only fall asleep in their mother's arms or the back seat of a moving vehicle. This results in excessive difficulty falling asleep or returning to sleep after awakening unless the specific condition or situation is met. Children, especially young children, naturally awaken at night and develop sleep-onset associations; the condition is only deemed a disorder if the association is highly problematic or disruptive or if the absence of the condition results in extensive waking periods.[4]

Another feature of childhood insomnia is inappropriate limit-setting. This feature occurs when bedtime stalling is reinforced or rewarded by inconsistent or lax resistance from a caregiver. A young child may ask for a glass of water, then a story, then a snack, *ad infinitum*; an older child or adolescent may play one more round of a video game. Since bedtime resistance and fears about going to sleep are extremely common, the situation is only deemed a disorder if it is excessively disruptive or problematic to the child or caregiver.[5]

Differential Diagnosis

A diagnosis of insomnia can, and often does, co-occur with other sleep, mood, and neurologic disorders, among many other health issues. An insomnia diagnosis occurs when insomnia symptoms exist independent of other factors or when insomnia symptoms persist despite the adequate treatment of comorbid disorders. For example, a person with sleep apnea on effective continuous positive airway pressure (CPAP) treatment who continues to experience prolonged awakenings will be diagnosed with an insomnia disorder.

TABLE 9-1 highlights brief case examples of sleep disorders in the differential diagnosis of insomnia. Patients with restless legs syndrome similarly have difficulty falling asleep or experience prolonged awakenings, but these symptoms are caused by an underlying urge to move the legs. For more information on restless legs syndrome, refer to the article "Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders," by Meena Khan, MD, FAASM,[6] in this issue of *Continuum*. In this situation, the insomnialike symptoms should resolve with treatment for restless legs syndrome. Circadian rhythm sleep-wake disorders can present similarly to insomnia disorders; people with a delayed sleep phase may have difficulty falling asleep at their desired bedtime, and those with an advanced sleep phase may have difficulty with early morning awakenings. In the case of circadian rhythm

Common Sleep Disorders to Consider in the Differential Diagnosis of Insomnia TABLE 9-1

Sleep disorder	Presentation
Restless legs syndrome	Difficulty falling asleep or maintaining sleep due to unpleasant creepy-crawly sensations in the legs that are worse at night, worse at rest, and relieved by movement
Delayed sleep phase syndrome	Difficulty falling asleep until the early morning or waking up before late morning or afternoon; no subjective sleep complaints when allowed to sleep in their optimal window; more common in adolescents and young adults
Advanced sleep phase syndrome	No trouble falling asleep but experiences habitual early-morning awakenings; may doze off before desired bedtime; more common in older adults
Habitual short sleep time	May have normal or prolonged sleep onset, sleeping 6 or fewer hours per night, but without daytime impairment or dysfunction
Obstructive sleep apnea	Frequent, and occasionally prolonged, nocturnal awakenings, often presenting as nocturia; may include symptoms of light or restless sleep, snoring, apneas, daytime sleepiness, or large body habitus
Insufficient sleep syndrome	Short sleep times, often without difficulty falling asleep or staying asleep and with significant daytime impairment or excessive daytime sleepiness

KEY POINTS

- Insomnia in pediatric populations often presents with inappropriate sleep-onset associations or limit-setting.
- Insufficient sleep syndrome, like insomnia, is characterized by reduced sleep time; however, with insufficient sleep syndrome sleep latency is typically short and sleep efficiency is high.
- While not necessary for a diagnosis of insomnia, a sleep study may be recommended to evaluate for suspected comorbid sleep apnea.
- Examples of insomnia perpetuating factors include excessive time in bed, an irregular sleep-wake schedule, rumination or excessive worry about sleep or daytime performance, unhelpful beliefs about sleep, and an overreliance on substances to help with sleep or alertness.

sleep-wake disorders, symptoms of insomnia should remit if the person sleeps within their biological sleep window. For more information on these disorders, refer to the article "Circadian Rhythm Sleep-Wake Disorders," by Flavia B. Consens, MD,[7] in this issue of *Continuum*.

Insufficient sleep syndrome, like insomnia, is characterized by reduced sleep time. However, with insufficient sleep syndrome sleep latency is typically short and sleep efficiency is high. In contrast with insomnia, a person with insufficient sleep syndrome will not spend excessive time in bed and will frequently have frank daytime sleepiness, a sign of their cumulative sleep debt.[8] For more information on sleep debt, refer to the article "Sleep Deprivation and Its Consequences," by Oleg Y. Chernyshev, MD, PhD,[9] in this issue of *Continuum*. A small subset of people have phenotypically natural short sleep phases and spend less than 6 hours asleep without apparent sleep dissatisfaction or daytime symptoms.[10]

Sleep apnea frequently co-occurs with insomnia, with 25% to 50% of obstructive sleep apnea diagnoses occurring in people who present with insomnia symptoms alone.[11,12] This overlap of conditions has been termed comorbid insomnia and sleep apnea (*COMISA*). Sleep apnea lightens and fragments sleep and causes significant daytime disturbance, the presentation and objective measurement of which can appear similar to insomnia.[13] While not necessary for a diagnosis of insomnia, a sleep study may be recommended to evaluate for suspected comorbid sleep apnea.

Pathophysiology

In contrast to other sleep disorders, there is no universally accepted pathophysiologic model of insomnia. This lack of consensus could be related to the heterogeneous nature of the disease or the subjective criteria for diagnosis. Nonetheless, the pathologic framework of insomnia has coalesced around the concept of hyperarousal. A state of hyperarousal disrupts the balance of sleep and wakefulness by creating a heightened physiologic, cognitive, or emotional response that interferes with the sleep process by preventing the disengagement of the waking brain from its environment.

3P Model of Insomnia

The 3P model (or Spielman model) of insomnia is the most widely accepted theoretical model of insomnia.[14] This model posits three underlying factors that lead to an insomnia disorder:

- Predisposing factors: underlying conditions or states that place someone at an elevated risk for developing insomnia, such as genetic dispositions, personality factors, environmental factors, or a combination of these factors.
- Precipitating factors: acute events that trigger an initial sleep difficulty that may result in short-term insomnia disorder, some of which are easily identifiable (eg, a traumatic event) and other contributors that are difficult to identify on retrospective history.
- Perpetuating factors: behavioral and cognitive factors that lengthen the course of insomnia, resulting in chronic insomnia (FIGURE 9-1).

Examples of perpetuating factors include excessive time in bed, an irregular sleep-wake schedule, rumination or excessive worry about sleep or daytime performance, unhelpful beliefs about sleep, and an overreliance on substances to

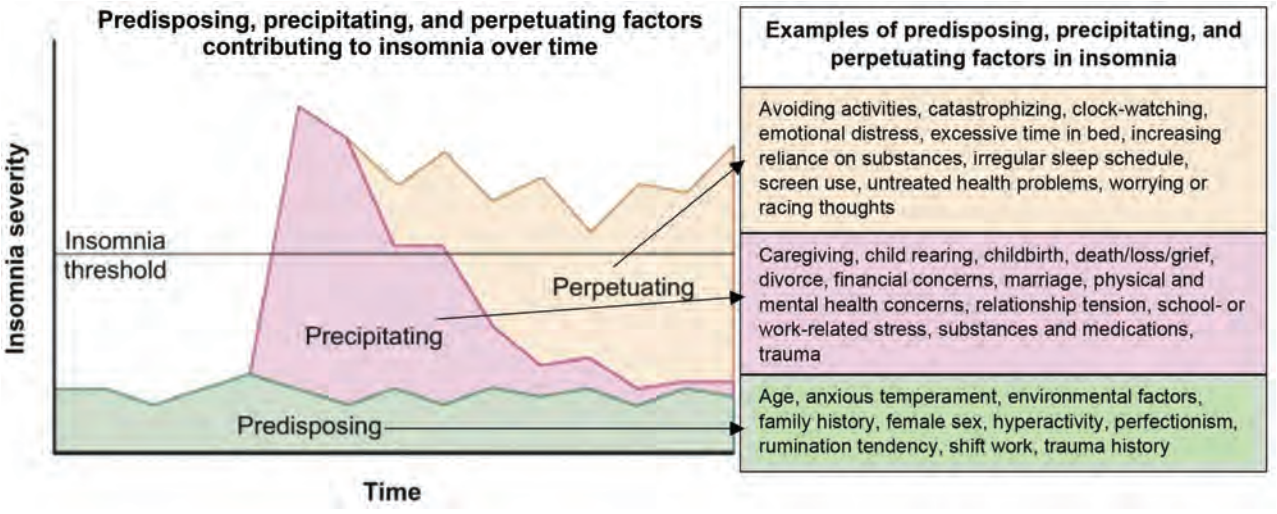

FIGURE 9-1
Overview of the predisposing, precipitating, and perpetuating factors that underlie the pathophysiology of insomnia based on the 3P model. Predisposing factors increase susceptibility to insomnia. Precipitating factors may lead to short-term insomnia symptoms. Perpetuating factors create the conditions for chronic insomnia disorder and are often the target of treatment.

help with sleep or alertness. Paradoxically, these factors are often responses to sleep effort or effort to control sleep due to anxiety about sleep and its consequences. Perpetuating factors are the primary target of cognitive behavioral therapy for insomnia (CBT-I).

Physiologic Changes and Diagnostic Findings

Studies evaluating physiologic changes in insomnia are limited by small sample sizes that are insufficient to clarify such a common and heterogeneous disorder. Some evidence supports an abnormal hyperarousal state underlying insomnia on genetic, molecular, cellular, and functional levels. Family and twin studies show evidence for the heritability of insomnia traits through multiple genes. Molecular studies have demonstrated differing levels of melatonin, γ-aminobutyric acid (GABA), cortisol, and adrenocorticotropic hormone in those with insomnia relative to controls.[15] People with insomnia may show evidence of hyperarousal that manifests in the form of an elevated heart rate, abnormal heart rate variability, an altered core body temperature, or the blunting of the decreased metabolic rate associated with non–rapid eye movement (non-REM) sleep.[16] Spectral EEG analysis, a method for assessing the frequency and strength of EEG signals over time, also demonstrates elevated beta and gamma activity during non-REM and REM sleep in people with insomnia.[17] Polysomnography (PSG) should not be used to confirm a diagnosis of insomnia. For those with insomnia and a suspected additional sleep disorder that warrants PSG evaluation, PSG may show prolonged sleep latencies, reduced sleep times, and increased wakefulness after sleep onset, although significant night-to-night variability can exist. A subset of people may experience a reverse first-night effect, where they sleep better in the sleep lab environment. In addition, a significant discrepancy between an objectively measured sleep time and a subjective report may occur. However,

health care professionals recognize this sleep-state misperception as a common feature in many people with and without insomnia.

CLINICAL MANAGEMENT OF INSOMNIA

Insomnia is a clinical diagnosis, although some validated tools and surveys can aid in diagnosing patients. In recent years, the focus of treatment has shifted from pharmacotherapy to nonpharmacologic interventions.

Assessment for Insomnia

The diagnosis of insomnia is made by a comprehensive clinical evaluation of sleep history (eg, symptom onset, duration, frequency, course, severity, daytime consequences, other sleep symptoms, previous treatment), current sleep patterns (eg, sleep-wake patterns, behaviors, environmental and relevant social factors), medical history (eg, comorbid pain syndrome), psychiatric history (eg, comorbid depression), and history of substance and medication use.[18] Self-report measures such as the Insomnia Severity Index,[19] Epworth Sleepiness Scale,[20] and the Dysfunctional Beliefs and Attitudes About Sleep Scale[21] can be administered as part of the clinical evaluation. Practitioners also recommend patients keep sleep diaries to track various important indices such as bedtime, estimates of sleep-onset latency, number of awakenings per night, wakefulness after sleep onset, early morning awakenings, final wake time, and rise time. Actigraphy is typically unnecessary for insomnia evaluation, although it can be beneficial to characterize circadian patterns, particularly among individuals who have difficulty reporting or tracking sleep-wake patterns using sleep diaries (eg, older adults with cognitive impairment). PSG is not indicated for insomnia evaluation unless a clinical suspicion exists for comorbid sleep-related breathing or movement disorders.

Treatment for Insomnia

Both pharmacologic and nonpharmacologic approaches can be effective in addressing insomnia. Nonpharmacologic approaches are considered first-line therapy, although medication may be indicated for certain patients.

NONPHARMACOLOGIC APPROACHES. The nonpharmacologic interventions for insomnia described below are effective with minimal side effects for adults, and these interventions can also be appropriate for adolescent populations. For information on the treatment of insomnia in pediatric populations, refer to the article "Sleep Disorders in Childhood," by Althea Robinson Shelton, MD,[22] in this issue of *Continuum*.

COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA. CBT-I, an evidence-based, time-limited, multicomponent intervention, is the first line of treatment for chronic insomnia in adults.[18,23] Standard CBT-I is delivered in four to eight weekly or biweekly sessions in an individual or group format, with session lengths of 30 to 90 minutes. Intervention components include sleep restriction, stimulus control, cognitive therapy, relaxation training, and sleep hygiene education. Sleep restriction aims to consolidate sleep by reducing the time spent awake in bed so that the time in bed approximates total sleep time based on sleep diary data. To identify the ideal amount of time spent in bed, practitioners commonly prescribe the average total sleep time plus an additional 30 minutes, although

individualized recommendations based on patient characteristics are warranted. Stimulus control is a set of recommendations aimed at strengthening the association between the bed and sleep. These include using the bed only for sleep and sex, going to bed when sleepy, minimizing lingering in bed in the morning, and getting out of bed after 20 minutes of wakefulness or when awake and feeling frustrated or worried. These practices are based upon principles of classical conditioning, ensuring that the bed remains a strong cue for sleep. Cognitive therapy uses psychoeducation, Socratic questioning, and behavioral experiments to challenge and reframe dysfunctional thinking patterns contributing to insomnia. This interactive process allows patients to recognize common sleep misperceptions and their associated costs through guided discoveries. Relaxation training teaches structured relaxation exercises to reduce nighttime arousal levels. Commonly taught exercises include diaphragmatic breathing, progressive muscle relaxation, and guided imagery. Finally, sleep hygiene education recommends habits that help maintain sleep without arousals, including increasing daytime activities, reducing daytime napping, and minimizing alcohol use prior to bedtime. Although poor sleep hygiene can contribute to insomnia, sleep hygiene instruction alone is not an effective treatment for insomnia. The combination of these intervention components is the key to improving insomnia symptoms (**CASE 9-1**).

Comparative effectiveness research on CBT-I, pharmacotherapy, and a combined CBT-I and pharmacologic approach shows greater long-term benefits derived from CBT-I alone or from CBT-I combined with pharmacotherapy than with pharmacotherapy alone.[24-28] Observational and clinical trial data show that CBT-I reduces the use of sedative-hypnotic medications overall.[29] Although the effects of CBT-I may attenuate over time, sleep improvements can remain up to a year after therapy.[30] Research also shows that CBT-I is effective in special populations, including adolescents,[31] older adults,[32] and individuals with medical and psychiatric comorbidities[33,34] such as depression,[35,36] anxiety,[37] chronic pain,[38] and heart failure.[39] Evidence exists that CBT-I improves alcohol dependency, depression, and posttraumatic stress disorder symptoms[33,40] in addition to improving sleep outcomes. Despite the strong evidence for CBT-I use, pharmacologic approaches remain the most prescribed treatment for insomnia. Access to care is another significant barrier due to shortages of trained CBT-I providers, treatment costs, and limited resources in underserved areas. Efforts to increase access to CBT-I include the development of brief behavioral treatment for insomnia and digital CBT-I, which are discussed later in this article.

BRIEF BEHAVIORAL TREATMENT FOR INSOMNIA. Brief behavioral treatment for insomnia is an abbreviated version of CBT-I that focuses on the behavioral components of CBT-I (ie, sleep restriction and stimulus control). Brief behavioral treatment for insomnia is a shortened version of CBT-I that includes flexible delivery methods ranging from one to four sessions delivered in person or via phone calls.[41] In contrast to CBT-I, which is typically delivered by doctoral-level clinicians with advanced training in behavioral sleep medicine, studies show that master-level clinicians (eg, nurses, social workers) can effectively provide brief behavioral treatment for insomnia.[42] These advantages enable brief behavioral treatment for insomnia to be better integrated into general medical settings, such as primary care. A randomized noninferiority

KEY POINTS

- **Insomnia is characterized by a state of global hyperarousal, which is reflected in the underlying pathophysiologic changes associated with the disorder.**
- **Polysomnography is not indicated for insomnia evaluation unless a clinical suspicion exists for comorbid sleep-related breathing or movement disorders.**
- **Cognitive behavioral therapy for insomnia is a time-limited multimodal therapy involving the common core principles of sleep restriction, stimulus control, and cognitive and relaxation training.**

clinical trial that compared the effects of CBT-I versus brief behavioral treatment for insomnia showed that both treatments effectively reduce insomnia symptoms. The difference between the treatment effects of CBT-I and brief behavioral treatment for insomnia was within the noninferiority margin, but the 95% confidence interval of the difference in treatment effects extended beyond the noninferiority margin and therefore this trial did not conclusively determine the noninferiority of brief behavioral treatment for insomnia to CBT-I.[43] While the data are inconclusive, health care providers can still use brief behavioral treatment for insomnia and include it in routine clinic visits given the brevity of the treatment.

MINDFULNESS-BASED INTERVENTIONS FOR INSOMNIA. Mindfulness-based interventions involve the teaching and practice of mindfulness meditations that

CASE 9-1

A 67-year-old woman presented to the neurology clinic with a concern about sleep onset and maintenance difficulties that started during the COVID-19 pandemic. The symptoms were exacerbated by social isolation stemming from the pandemic. She had been taking zolpidem 10 mg nightly for 6 months. The perpetuating factors for her insomnia included increased time spent in bed, resting and using her phone in bed during the day, and watching TV news about the pandemic prior to bedtime. She also had anxiety about the effects of insomnia on her daytime functioning. She tracked her sleep using a sleep diary to establish a baseline, with an average total sleep time of 6 hours (FIGURE 9-2A). To reduce her time in bed, the neurologist recommended she maintain a 6.5-hour sleep window from 12:00 AM to 6:30 AM, as well as a morning routine with increased daylight exposure to help her consistently get out of bed at the same time. During the day, she was encouraged to stay outside of her bedroom and engage in more physical and pleasant activities, such as gardening and walking. In the evening, her neurologist recommended that she develop a wind-down routine with reduced screen use and news consumption. To help calm her mind, her neurologist introduced her to diaphragmatic breathing and coping statements that she could use when feeling anxious and lying awake at night (eg, "I will get through tomorrow just like before."). The patient's sleep eventually improved with a sleep-onset latency of less than 30 minutes and an increased trust in her sleep system. Her neurologist instructed her to reduce her zolpidem use by 25% per week, cautioning her that rebound insomnia may occur. After discontinuing zolpidem, her sleep patterns remained appropriate, with brief awakenings (FIGURE 9-2B). Her neurologist reminded her that brief awakenings were normal. However, given a history of snoring as observed by her bed partner, her neurologist also recommended that she consult with her primary care provider or sleep medicine physician to evaluate for possible obstructive sleep apnea as a contributing factor to her nocturnal awakenings.

help cultivate a person's nonjudgmental and intentional awareness of thoughts, emotions, bodily sensations, and other experiences in the moment. In the context of insomnia, this approach allows individuals to observe their experience during undesired waking states in a kind and compassionate manner, helping them let go of their attachment to sleep and reduce their effort to achieve sleep. This approach is consistent with the metacognitive model of insomnia,[44] which suggests secondary arousals caused by one's reactions to sleep-related thoughts and beliefs as key factors perpetuating insomnia. Randomized controlled trials and reviews of such trials show positive treatment effects of mindfulness-based interventions, such as improved sleep quality and insomnia severity.[45] However, the current body of evidence is insufficient to recommend mindfulness-based interventions as a first-line treatment for insomnia.[46]

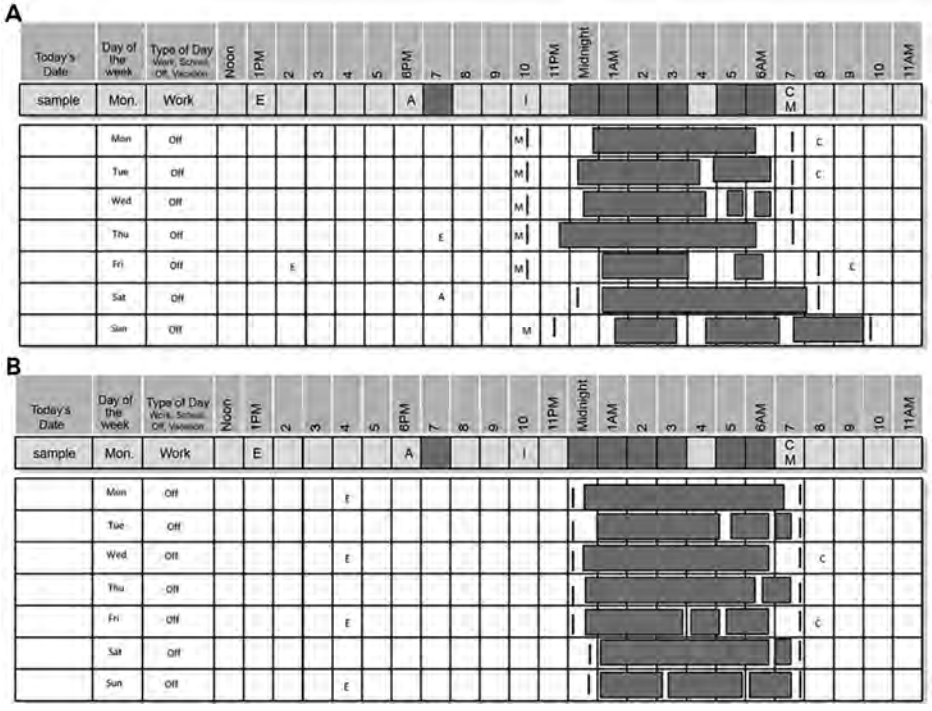

FIGURE 9-2

Sleep diary for the patient in CASE 9-1, showing the patient's recorded sleep data pretreatment (*A*) and posttreatment (*B*). Vertical lines (|) represent the patient's bed and wake-up times.

A = alcohol use; C = caffeine intake; E = exercise; M = medication for sleep.

COMMENT

This case exemplifies the treatment elements of cognitive behavioral therapy for insomnia and the dynamic process of collaborating with patients to develop a feasible treatment plan.

KEY POINTS

- Cognitive behavioral therapy for insomnia alone or in combination with medication is more effective for insomnia than medication alone.
- Most US Food and Drug Administration (FDA)-approved medications for insomnia work via the modulation of $GABA_A$ receptors, which are targets of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter for the central nervous system.
- Benzodiazepines are not recommended for older adults due to the increased risks of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes.

PHARMACOLOGIC APPROACHES AND PHARMACOTHERAPY. Pharmacotherapy for insomnia can work in one of two ways: increase the sleep signal or decrease the arousal signal. Patients and clinicians might not always consider these processes during medication selection; even when considering these factors, finding the right drug at the right dose can be challenging (CASE 9-2). In a 2017 consensus statement, none of the 14 medications and supplements reviewed achieved better than a weak recommendation for the treatment of sleep-onset or sleep-maintenance insomnia,[47] which highlights the overall limitations of pharmacologic treatment for insomnia.

In general, starting medication is a clinical judgment between a patient and their treating clinician. Factors to consider include the duration and frequency of dosing (eg, standing or intermittent dosing, time-limited versus ongoing prescription), patient age and sex, comorbid medical conditions, and concurrent medications. In all cases, the clinician should try to provide CBT-I and should consider and evaluate for other sleep disorders as indicated.

A summary of the medications covered in this section is shown in TABLE 9-2. Most of these medications, including those approved by the US Food and Drug Administration (FDA) for the treatment of insomnia, work by modulating GABA, orexin (hypocretin), histamine, or melatonin neurotransmitter systems. Several commonly used off-label medications work via these or other neurochemical pathways.

Published reviews provide a treatment algorithm for prescribing sleep aids.[18] Clinicians and patients should acknowledge the limitations of medications for insomnia, understand the importance of individualizing therapy, and make a concerted shift toward CBT-I for the treatment of chronic insomnia. Ten of the medications covered in this article received a moderate recommendation to avoid use by the American Geriatrics Society 2019 Beers criteria due to adverse effects.[44] Prescribing clinicians should understand the medication classes and mechanisms of action to guide their patients in making an informed treatment decision.

γ-AMINOBUTYRIC ACID. Most FDA-approved medications for insomnia work via the modulation of $GABA_A$ receptors, which are targets of GABA, the primary inhibitory neurotransmitter for the central nervous system. Relevant medications include the benzodiazepines triazolam and temazepam, along with a class of medications that includes zolpidem, eszopiclone, and zaleplon which act as nonbenzodiazepine agonists of GABA receptors. These latter three drugs, as well as the associated long-acting and low-dose formulations of zolpidem, have selectivity for the $GABA_A$ receptor found in higher concentrations in the ventrolateral preoptic nucleus, the major sleep-active nucleus of the hypothalamus.

The benzodiazepine drugs triazolam and temazepam were among the first medications approved for the treatment of insomnia. Both medications show reductions in sleep latency and increases in total sleep time.[28] Benzodiazepine drugs should not be considered as first-line treatments and should only be considered for short-term use due to their prolonged half-lives and adverse effects that include sedation, dizziness, falls, and dependency. Benzodiazepines are generally not recommended for older adults due to the increased risks of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes.[48]

Among the nonbenzodiazepine GABA receptor agonists approved for prolonged middle-of-the-night awakenings are zolpidem (5 mg and 10 mg at bedtime), extended-release zolpidem (6.25 mg and 12.5 mg every night at

CASE 9-2

A 48-year-old woman presented with difficulty falling asleep and staying asleep. Her sleep problems had been lifelong but worsened 4 years ago when she became a partner at a busy law firm. She reported taking hours to fall asleep, with a total sleep time of 2 to 3 hours per night. She believed poor sleep had led to fatigue, lower productivity, and the inability to exercise, and she had developed significant concerns about being fired. She could not nap, although she was extremely tired. She went to bed around 9:30 PM, with a sleep-onset latency of 2 to 3 hours and two to three awakenings per night, each lasting 15 to 60 minutes. She frequently worked until bedtime. When awake at night, she reported racing thoughts about work and sometimes checked her work email while in bed. She often awoke before her alarm at 7:30 AM and would lie in bed and try to fall back asleep until her alarm sounded. She had previously taken zolpidem, zolpidem-controlled release, temazepam, zaleplon, and lorazepam, none of which improved her symptoms. She had also tried melatonin doses of up to 20 mg daily. She purchased blackout curtains and a new mattress without subsequent symptomatic benefit. She reported drinking two to three cups of coffee daily, with her last cup by 2:00 PM, and having two to four alcoholic drinks per week. She had no history of snoring, urges to move her legs before bedtime, or abnormal behaviors or dreams while asleep. She was desperate to have better sleep.

COMMENT

This patient's symptoms are consistent with chronic insomnia, with elements that are frequently encountered in the clinical setting. She had a clear predisposing factor (lifelong propensity for poor sleep) and precipitating factor (work stress). She also exhibited classic perpetuating factors, which included spending excessive time in bed, reliance on caffeine, and rumination about sleep and work performance. Her self-estimated sleep times suggested an element of sleep-state misperception; the degree of chronic sleep deprivation reported would leave her significantly more debilitated than her performance indicates.

Clinicians should reassure patients with insomnia that their condition is treatable, as patients may feel desperate or hopeless; chronic insomnia is a common condition that can be successfully treated. The multiple medications the patient tried worked mechanistically to affect either γ-aminobutyric acid (GABA) or melatonin. One treatment consideration could include medications such as dual orexin receptor antagonists or sedating antidepressants that inhibit waking neurotransmitters such as orexin (hypocretin) or histamine. While it is laudable that she made multiple efforts to improve her sleep hygiene, it is important to note that sleep hygiene strategies alone are insufficient to treat chronic insomnia. An appropriate next step would be cognitive behavioral therapy for insomnia, with an initial focus on sleep restriction, stimulus control, and mindfulness practices.

bedtime), and sublingual zolpidem (1.75 mg and 3.5 mg at bedtime). Among this class, eszopiclone (1 mg to 3 mg at bedtime) has the longest half-life, while zaleplon (5 mg and 10 mg at bedtime) has the shortest half-life and thus is recommended only for sleep-onset difficulties.

Across many treatment guidelines, the nonbenzodiazepine GABA receptor agonist medications are considered first-line therapies when medication is indicated,[18] and clinicians may tailor treatment to individual sleep symptoms (ie, greater difficulty with sleep onset, maintenance, or both). In cases of treatment

TABLE 9-2 **Common Sleep-Promoting Agents Used in the Treatment of Insomnia**

Medication class and agent	Related neurotransmitter system	Dose range	Half-life	FDA approved for treatment of insomnia	Requires prescription	Appropriate for people >65 years old by Beers criteria
Antihistamine						
Diphenhydramine	Histamine	12.5 mg to 50 mg	3.4 h to 9.2 h	No	No	No
Hydroxyzine	Histamine	50 mg to 100 mg	7 h to 20 h	No	Yes	No
Antipsychotic						
Quetiapine	Histamine/ serotonin	25 mg to 100 mg	6 h	No	Yes	Yes
Benzodiazepine						
Temazepam	GABA	7.5 mg to 30 mg	3.5 h to 18 h	Yes	Yes	No
Triazolam	GABA	0.125 mg to 0.5 mg	1.5 h to 5.5 h	Yes	Yes	No
Benzodiazepine receptor agonist						
Eszopiclone	$GABA_A$	1 mg to 3 mg	6 h to 9 h	Yes	Yes	No
Zaleplon	$GABA_A$	5 mg to 20 mg/day	0.5 h to 1 h	Yes	Yes	No
Zolpidem	$GABA_A$	5 mg to 10 mg	2.5 h	Yes	Yes	No
Zolpidem ER	$GABA_A$	6.25 mg to 12.5 mg	2.8 h	Yes	Yes	No
Dual orexin receptor antagonist						
Daridorexant	Orexin (hypocretin)	25 mg to 50 mg	8 h	Yes	Yes	Yes
Lemborexant	Orexin (hypocretin)	5 mg to 10 mg	17 h to 19 h	Yes	Yes	Yes

CONTINUED ON PAGE 1179

nonresponse, these medications may be considered sequentially, although they should not be used in combination.

As with benzodiazepine drugs, the nonbenzodiazepine GABA receptor agonists are not recommended for older adults for similar reasons.[44] The FDA recently issued several statements of caution about the adverse effects of benzodiazepine receptor agonist drugs. The FDA now recommends reducing the maximum doses of these medications for women and people 65 years old and older to 5 mg (zolpidem), 6.25 mg (extended-release zolpidem), 2 mg

CONTINUED FROM PAGE 1178

Medication class and agent	Related neurotransmitter system	Dose range	Half-life	FDA approved for treatment of insomnia	Requires prescription	Appropriate for people >65 years old by Beers criteria
Suvorexant	Orexin (hypocretin)	5 mg to 20 mg; trials studied up to 40 mg (30 mg in people ≥65 years old)	12 h	Yes	Yes	Yes
Exogenous melatonin						
Melatonin	Melatonin	1 mg to 5 mg	20 min to 40 min	No	No	Yes
α2δ Ligands						
Gabapentin	Calcium channel blockade	100 mg to 600 mg	5 h to 7 h	No	Yes	Yes
Melatonin receptor agonist						
Ramelteon	Melatonin	8 mg	1 h to 2.6 h	Yes	Yes	Yes
Sedating antidepressant						
Amitriptyline	Histamine/ serotonin	10 mg to 100 mg	31 h to 46 h	No	Yes	No
Doxepin	Histamine	3 mg to 6 mg	15 h	Yes	Yes	Yes
Mirtazapine	Histamine	7.5 mg to 30 mg	20 h 40 h	No	Yes	Yes
Trazodone	Histamine/ serotonin	25 mg to 200 mg	5 h to 9 h	No	Yes	Yes

ER = extended release; FDA = US Food and Drug Administration; GABA = γ-aminobutyric acid.

(eszopiclone), and 5 mg (zaleplon); these dose recommendations are lower than that for men and people under 65 years old. The FDA issued these recommendations because of concerns about higher residual plasma concentrations,[48] which can potentially lead to excessive residual morning sedation and dangers when operating heavy machinery, including motor vehicles. The potential for complex injurious behaviors with an amnestic component exists, including eating, wandering, and driving (reported in up to 3% of people).[49] These medications contain a boxed warning for their use in patients with a history of complex parasomnias.

OREXIN (HYPOCRETIN). Orexin (hypocretin) is released from a small subset of cells in the posterior hypothalamus, the autoimmune destruction of which is responsible for narcolepsy type 1. For information on the relationship between orexin (hypocretin) and narcolepsy, refer to the article "Central Disorders of Hypersomnolence," by Margaret Blattner, MD, PhD, and Kiran Maski, MD, MPH,[50] in this issue of *Continuum*. The binding of orexin (hypocretin) neuropeptides A and B results in the upregulation of dopaminergic, histaminergic, cholinergic, and noradrenergic pathways, which causes arousal and sustained wakefulness. The new dual orexin receptor antagonists induce sleep by blocking the orexin (hypocretin) system. There are now three available drugs in this class: suvorexant, lemborexant, and daridorexant. All three have demonstrated efficacy in reducing sleep-onset latency, reducing wake-after-sleep onset, and increasing total sleep time.

Suvorexant, the first available dual orexin receptor antagonist, can be dosed at 5 mg, 10 mg, and 20 mg, although clinical trials initially focused on higher doses of up to 40 mg (30 mg in people ≥65 years old) for an efficacy range.[51] Trials have shown similar alertness thresholds[52] and reaction times[53] during middle-of-the-night awakenings in patients taking suvorexant versus placebo, in contrast to the sedation noted with benzodiazepines and nonbenzodiazepine GABA receptor agonists. Lemborexant has demonstrated improved sleep latency and wake-after-sleep onset.[54] Daridorexant, the newest dual orexin receptor antagonist, has a significantly shorter half-life. The most common adverse effect of dual orexin receptor antagonists is somnolence (13%). Given their action on orexin (hypocretin), dual orexin receptor antagonists have the potential to induce narcolepsylike symptoms, including sleep paralysis and hypnagogic and hypnopompic hallucinations, which occur in less than 1% of patients.[55] Mouse models have demonstrated cataplexy with dual orexin receptor antagonist use, and cataplexy is possible in those taking dual orexin receptor antagonists, although it is extremely rare.

While much of the research about dual orexin receptor antagonists focuses on the relative safety and tolerability of these medications in people 65 years old and older,[56] it should be noted that nonbenzodiazepine GABA receptor agonists were once similarly promoted in comparison to benzodiazepines; it took several years before prescribers were alerted to the concerning adverse effects of nonbenzodiazepine GABA receptor agonists.

HISTAMINE. Histamine is released from the tuberomammillary nucleus and is among the neurotransmitters that induce wakefulness. Selective blockage of histamine receptors alone is an effective mechanism for inducing and maintaining sleep. Most sedating antidepressants work, at least partially,

through histamine antagonism. Trazodone and amitriptyline also work through noradrenergic and serotonergic pathways. Low doses of mirtazapine and doxepin appear highly selective for brain histamine 2 receptors,[57] more so than even the antihistamine medications diphenhydramine and hydroxyzine.

Trazodone, 25 mg to 150 mg, is among the most prescribed sedating antidepressants, likely because of its lack of addiction potential.[58] Doxepin, 3 mg, is the only sedating antidepressant that is FDA approved for the treatment of insomnia. However, it may be prescribed at 10 mg because of the lower cost of the 10-mg dose.[59] Mirtazapine, 7.5 mg to 15 mg, acts similarly to doxepin, although it may have more effects on depression and exhibit more adverse effects (including potential for weight gain) at lower doses.[60] Overall, the use of sedating antidepressants may be tailored to individual patients depending on comorbidities including depression, anxiety, or pain.

While diphenhydramine and hydroxyzine have the sedating qualities of antihistaminergic antidepressants, they have less demonstrated efficacy on objective sleep measures.[61] In addition, these medications have higher rates of adverse effects, including sedation (owing to their anticholinergic properties), and an association with dementia.[62]

MELATONIN. Melatonin is released endogenously by the pineal gland and promotes sleep by acting on MT_1 and MT_2 receptors in the suprachiasmatic nucleus. Exogenous melatonin, which is regulated as a supplement in the United States, also works through this mechanism. Ramelteon, 8 mg, acts as an MT_1 and MT_2 receptor agonist with higher affinity than endogenous melatonin. Melatonin may be more effective for the treatment of circadian rhythm sleep-wake disorders than for insomnia[7]; when used as a hypnotic, melatonin and melatonin receptor agonists have relatively short half-lives that make them more suitable for inducing sleep onset rather than supporting sleep maintenance, for which they have only shown mild benefit.[63] In addition, the clinician should consider whether the primary aim of melatonin treatment is as a hypnotic or a chronobiotic, as different intended uses have distinct dosing regimens and timings of administration.[7]

Because exogenous melatonin is classified as a supplement, innumerable varieties and formulations exist, including slow-release forms that may provide more benefit for sleep maintenance insomnia. One or more supplements or herbs are often combined with melatonin. A melatonin dose of 1 mg to 5 mg is a typical starting dose, although melatonin is often found in doses of 10 mg or higher. Adverse effects can include headaches, nightmares, mood changes, and paradoxical insomnia. Given the lack of FDA regulation, there is dose heterogeneity across and within brands, with actual pill contents varying from 83% less to nearly 500% more melatonin than advertised.[64] Safety concerns exist about using an unregulated hormone that affects a wide range of bodily functions outside of sleep, the effects of which have been largely unstudied.

OTHER PHARMACOLOGIC TREATMENTS. The α2δ ligand gabapentin reduces the release of wake-promoting neurotransmitters via the modulation of calcium channels. A limited number of studies with small sample sizes yielded evidence that gabapentin can reduce nocturnal awakenings, improve sleep efficiency, and increase slow-wave sleep.[65] Small studies have also suggested that gabapentin may improve sleep quality in children.[66] As with the sedating antidepressants

KEY POINTS

- Given their action on orexin (hypocretin), dual orexin receptor antagonists have the potential to induce narcolepsylike symptoms, including sleep paralysis and hypnagogic and hypnopompic hallucinations, which occur in less than 1% of patients.
- Low doses of mirtazapine and doxepin appear highly selective for brain histamine 2 receptors, more so than even the antihistamine medications diphenhydramine and hydroxyzine.
- Given the lack of FDA regulation of exogenous melatonin, there is heterogeneity of doses across and within brands, with actual pill contents that vary from 83% less to nearly 500% more melatonin than advertised.

mentioned above, gabapentin may be most useful for insomnia with comorbidities such as neuropathy or restless legs syndrome.

Quetiapine is a second-generation antipsychotic medication that antagonizes multiple neurotransmitters and may exert sleep effects mediated by serotonin and histamine. There is limited evidence regarding the efficacy of quetiapine for insomnia.[67] Although both gabapentin and quetiapine are considered safe at the lower doses typically used for insomnia, they can potentially induce metabolic changes such as weight gain and mood changes including suicidal ideation.

PLACEBO. One meta-analysis suggested that the placebo effect alone can account for up to 50% of measured changes in randomized controlled trials in people with insomnia.[68] However, open-label placebo trials to date have not shown effectiveness in this population.[69] This phenomenon must simply be recognized and acknowledged, rather than exploited, with more work still to be done in this area.

Technology Tools in the Clinical Management of Insomnia

Technologic advances offer new opportunities for health care and also present challenges for clinicians. This section reviews how technology may be used in the clinical management of insomnia.

TELEHEALTH. The use of telehealth, which includes clinical services delivered remotely via videoconferencing, increased rapidly during the COVID-19 pandemic and is expected to continue to grow. A survey of health care professionals in sleep medicine showed that few virtual visits were offered before the pandemic; in contrast, three-quarters of sleep medicine clinics exclusively used virtual visits during the survey period of April 2020 through May 2020.[70] The survey also indicated that approximately one-half of the providers believed that 25% or more of their practice would be delivered via telehealth in the future. Data from a recent randomized controlled noninferiority trial suggest that CBT-I delivered through telehealth is comparable to in-person delivery.[71]

DIGITAL COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA. Recent developments include the growth of digital CBT-I, defined as CBT-I delivered via computers, the internet, mobile applications, and other devices. A meta-analysis of randomized controlled trials found that digital CBT-I is effective for insomnia treatment in adults.[72] The few available noninferiority trials showed larger treatment effects of in-person CBT-I than digital CBT-I; the difference was within the noninferiority interval, suggesting that digital CBT-I is noninferior to the standard delivery of CBT-I. Considerable heterogeneity exists among digital CBT-I programs, as there are varying levels of clinical support that range from fully automated digital CBT-I programs to adjunctive tools that enhance clinician-delivered CBT-I. An earlier meta-analysis showed that a higher degree of personal clinical support in digital CBT-I programs was associated with better outcomes,[73] although a more recent meta-analysis did not show the same result.[72] It is possible that technologic advances have improved the quality of automated personalized feedback. Regardless of the degree of clinician participation, digital CBT-I programs reduce time spent with clinicians and are thus less expensive to deploy and more scalable to a wider population. Several key issues require further investigation: long-term outcomes, effectiveness among individuals with

psychiatric and medical comorbidities, and the uptake of, and adherence to, digital CBT-I programs. As efforts to disseminate digital CBT-I continue, it is critical to prevent a widened digital divide among populations with limited access to computers or the internet, such as older adults, individuals with disabilities, individuals living in rural areas, and individuals of lower socioeconomic status.

CONSUMER SLEEP TECHNOLOGIES. Consumer devices that use wearable or embedded sensors to track movement and other biometric indices to estimate sleep-wake timings in the home environment are increasingly popular due to novelty, convenience, and affordability. Clinicians encounter a growing number of patients who present with questions and concerns about data from their consumer sleep-tracking devices. This scenario presents both opportunities and challenges in the clinical management of insomnia.

Consumer sleep technologies should not be used for diagnosis or to replace preferred treatments given the lack of validation data, absence of FDA clearance, and limited access to raw data and proprietary algorithms.[74] Overreliance on such devices may have unintended clinical consequences, such as an underestimation of sleep problems that result in delayed clinical care or an overestimation of sleep problems that result in unnecessary distress. In fact, clinicians observe orthosomnia, or preoccupation with achieving optimal sleep, more frequently among patients who are rigid about the accuracy and utility of sleep-tracking data.[75]

However, the use of consumer sleep technologies may be beneficial with appropriate clinical evaluations and support. These technologies can potentially increase patient awareness about sleep health, allow patients to access real-time and visual data in response to their sleep-related behaviors, and serve as an alternative tool to self-reported sleep diaries. This in-the-moment feedback can increase motivation and engagement for treatment. Despite these potential benefits, it remains unclear if tracking sleep via wearable devices improves treatment outcomes more than self-reported sleep diaries. Preliminary findings indicate that treatment effects do not differ between participants who used wearable devices versus those who did not.[76,77] When wearable devices were self-selectively used, as opposed to randomly assigned, wearable device users had more severe insomnia symptoms at baseline and posttreatment than nonusers.[8] These results dovetail with findings that indicate that sleep-tracking devices are more desirable among individuals with short sleep duration, greater sleep disturbances, and comorbid sleep disorders.[78] Since consumer sleep-tracking devices are advertised as tools to improve sleep, limited data on the efficacy of these programs highlight a potential mismatch between the user's desire for improved sleep and the device's ability to improve sleep. Nevertheless, as technology improves and more validation data become available, consumer sleep technologies may play a larger role in clinical settings. This evolution will require clinicians to become familiar with discussions around the use and limitations of consumer sleep devices.

KEY POINTS

- **Digital cognitive behavioral therapy for insomnia shows promise as an efficient and cost-effective way of delivering therapy to a large number of people, although efforts to increase access to care for individuals with limited access to computers or smartphones are still needed to prevent worsening a digital divide.**
- **Consumer sleep technologies may increase awareness of sleep health and sleep disorders, although they may contribute to excessive worry about sleep and should not be used as diagnostic tools by themselves.**

CONCLUSION

Insomnia is a commonly encountered condition affecting pediatric and adult populations and is seen at even higher rates in those with neurologic and

psychological disorders. Insomnia is best described as a disorder of hyperarousal and is defined by its subjective disruption to sleep and associated daytime sequelae. Several medications and supplements are often used to treat insomnia, although their effect is universally small, and there are significant concerns about their short-term and long-term neurocognitive adverse effects. This recognition has shifted the treatment focus from medication to nonpharmacologic approaches such as CBT-I, which has proven effective and adaptable to a digital format. This shift is likely to continue, although widespread adoption may be limited by a lack of access to trained providers. Deliberate efforts are needed to ensure that this shift to nonpharmacologic insomnia treatment improves care for all and does not exacerbate disparities in access to care. A greater understanding of the physiologic underpinnings that underlie insomnia may lead to further advances in accessible, evidence-based treatments.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Sleep Disorders in Patients with Neurologic Disease

By Joyce K. Lee-Iannotti, MD

ABSTRACT

OBJECTIVE: **This article provides an overview of the growing body of evidence showing bidirectional relationships between sleep and various neurologic disorders.**

LATEST DEVELOPMENTS: **Mounting evidence demonstrates that disrupted sleep can negatively impact various neurologic disease processes, including stroke, multiple sclerosis, epilepsy, neuromuscular disorders including amyotrophic lateral sclerosis, and headache syndromes. Abnormal sleep can also be a precursor to Alzheimer disease and neurodegenerative disease states such as Parkinson disease and dementia with Lewy bodies. Interventions to improve sleep and treat obstructive sleep apnea may play a vital role in preventing neurologic disease development and progression.**

ESSENTIAL POINTS: **Sleep disorders are common among patients with neurologic disorders. To provide comprehensive care to patients with neurologic conditions, neurologists must ask patients about sleep issues that may warrant further diagnostic testing, treatment, and sleep medicine referral when indicated.**

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INTRODUCTION

Sleep is essential for overall health and well-being; sleep dysfunction reduces quality of life and increases morbidity and mortality.[1] Sleep disorders may be more prevalent in patients with neurologic diseases, suggesting a potential bidirectional relationship between sleep and brain health. The mechanisms for sleep arise from the central nervous system and involve complex interplays between cellular and molecular mechanisms. Neurologic disorders, namely, stroke, epilepsy, and neurodegenerative diseases, can interfere with underlying circadian rhythms and sleep-wake regulation, resulting in symptoms such as insomnia and hypersomnia.

Disordered sleep can also increase the risk of neurologic disorders, including cerebrovascular disease, Parkinson disease, and Alzheimer disease. Recognition and treatment of underlying sleep disorders will likely improve overall quality of life and outcomes in patients with neurologic disease.

STROKE

Stroke is a leading cause of serious, long-term disability and is the second leading cause of death worldwide.[2] Acute treatment options, including IV thrombolysis and endovascular therapy, have revolutionized stroke care, but risk factor modification remains imperative in both primary and secondary stroke prevention. Obstructive sleep apnea is a recognized stroke risk factor, in addition to other risk factors including hypertension, diabetes, hyperlipidemia, tobacco use, and sedentary lifestyles.

Obstructive Sleep Apnea and Risk of Stroke

Obstructive sleep apnea (OSA) is a well-established independent risk factor for stroke.[3] OSA is associated with a twofold increased risk of incident stroke (relative risk 2.10; 95% confidence interval 1.50 to 2.93).[4] A large prospective population study, the Sleep Heart Health Study, followed approximately 5000 patients for 8 years and found that OSA increased the risk of stroke, particularly in men with moderate-to-severe OSA (adjusted hazard ratio of 2.86; 95% confidence interval 1.1 to 7.4).[5] Sleep-disordered breathing, defined as an apnea-hypopnea index score of greater than 5 events per hour, was present in up to 72% of patients with ischemic and hemorrhagic stroke and transient ischemic attack, compared to a prevalence range of 9% to 38% in the general population.[6] Subgroup analysis found that sleep-disordered breathing occurred more frequently in men, those with recurrent rather than initial stroke, and those with unclear stroke etiology (cryptogenic strokes).[6] Prior studies showed that neither event type (ischemic stroke, hemorrhagic stroke, or transient ischemic attacks) nor lesion location greatly impacts sleep-disordered breathing rates or severity.[7,8] However, a more recent meta-analysis demonstrated that the prevalence of OSA appeared to be greater in patients with cardioembolic strokes (cardioembolic: 74.3%; large artery atherosclerosis: 68.3%; small vessel occlusion: 56.1%; other or unknown causes: 47.9%), strokes that were supratentorial in location (67.9% versus 56.5%), and in the acute-subacute phase of stroke (acute 68.4% versus subacute 71.3% versus chronic 60.6%).[9]

The pathophysiologic mechanisms of OSA as a risk factor for stroke are increasingly understood through the evolving literature. The proposed mechanisms of stroke and OSA include endothelial dysfunction, oxidative stress, systemic inflammation, development of atherosclerosis linked to intrathoracic pressure swings, recurrent arousals and intermittent hypoxia resulting in sympathetic activation, development of cardiac arrhythmias (namely, atrial fibrillation), increased hypercoagulability, and reopening of pathologic cardiac shunting through a patent foramen ovale.[10-13] The presence of OSA has also been linked to individual risk factors for stroke, including diabetes,[14] hypertension,[15] and atrial fibrillation.[16,17] The early morning predilection of both atrial fibrillation and wake-up strokes also supports a causal relationship.[18]

Untreated OSA is also linked to higher incidences of recurrent strokes. In the Brain Attack Surveillance in Corpus Christi (BASIC) project, 526 of 842 participants (63%) with sleep apnea (apnea-hypopnea index score >10 events/hour) suffered recurrent strokes with an adjusted hazard ratio of 1.02 per one-point increase in the apnea-hypopnea index score (95% confidence interval 1.01 to 1.03).[19] The presence of OSA also increases poststroke mortality, with a trend analysis finding a correlation between increasing OSA severity and poorer outcomes.[20] A similar finding of increased mortality in patients with moderate

KEY POINTS

- Sleep apnea is a well-established independent risk factor for both initial and recurrent strokes.
- Almost three-quarters of people with stroke have poststroke sleep apnea.
- Obstructive sleep apnea has also been linked to individual risk factors for stroke, including diabetes, hypertension, and atrial fibrillation.
- Untreated sleep apnea can increase the risk of recurrent cerebrovascular events.
- Screening for sleep apnea in stroke patients remains underutilized, indicating a need for greater awareness about obstructive sleep apnea as a risk for recurrent strokes.

OSA (apnea-hypopnea index score >15 events/hour) admitted for in-hospital stroke rehabilitation was seen in a 10-year longitudinal study.[21]

Poor screening for OSA before and after stroke remains a major barrier to improving outcomes in patients with stroke. In the BASIC project, only 17% and 6% of participants were offered sleep evaluation or testing prestroke and poststroke, respectively.[22] Therefore, better education and organizational advocacy for OSA screening should be implemented within clinical guidelines for both primary and secondary stroke prevention.

Obstructive Sleep Apnea Treatment and Impact on Stroke Prevention

Continuous positive airway pressure therapy (CPAP) remains the consensus best treatment for moderate to severe OSA.[23] CPAP has been shown to decrease systolic and diastolic blood pressure,[24] decrease inflammatory markers associated with stroke,[25] and improve cerebral blood flow seen on color Doppler sonography.[26] The Sleep Apnea Cardiovascular Endpoints (SAVE) study investigated stroke incidence in 2717 participants 45 to 75 years old who had moderate to severe OSA and cardiovascular or cerebrovascular disease. Half of the subjects were randomized to receive CPAP plus usual care, while the other half were assigned to usual care alone. With a mean follow-up period of 3.7 years, no difference in stroke incidence was seen between the two groups. However, only 42% of participants randomized to CPAP were considered adherent with therapy (minimum of 4 hours of CPAP use per night) with a mean overall adherence of 3.3 hours per night. Additionally, the study participants were mostly of Asian descent, potentially limiting generalizability, and the study design excluded patients with excessive daytime sleepiness, which is the group most likely to benefit from intervention. Of note, propensity score-matched analysis of those fully adherent to CPAP showed lower stroke risk than those who received usual care. Ultimately, the design of the study did not sufficiently address the role of CPAP therapy in stroke prevention. Of note, secondary endpoints of reduced daytime hypersomnolence, reduced anxiety and depression, and overall improvement in quality-of-life measures were improved in the CPAP plus usual care treatment arm (**CASE 10-1**).[27]

Larger clinical trials are needed to assess stroke prevention from CPAP therapy. The Sleep for Stroke Management and Recovery Trial (Sleep SMART) is a phase 3, multicenter trial that randomizes patients with OSA in addition to acute stroke or transient ischemic attack to CPAP therapy plus usual care versus usual care alone. The outcomes of this study include recurrent stroke risk, acute coronary syndrome, all-cause mortality, and 3-month functional outcomes measured by the modified Rankin Scale score.[28] The results of this study are likely to shed light on the potential utility of expedited poststroke sleep testing and treatment.

Alternative Obstructive Sleep Apnea Treatments

Although CPAP is the consensus best treatment for patients with OSA, greater understanding of varying phenotypes and endotypes[29] in patients makes it clear that it may not be the only option for everyone and alternative therapies may be more appropriate. Alternative OSA treatments have not been widely studied in patients with stroke, but a few cases and small studies have shown some promise. A 6-week program of oropharyngeal muscle (ie, soft palate, tongue, facial) exercises in 25 patients poststroke with moderate OSA (apnea-hypopnea index

CASE 10-1

A 73-year-old right-handed man with a history of hypertension, hyperlipidemia, coronary artery disease with three prior drug-diluting stents, and paroxysmal atrial fibrillation sustained an acute large left middle cerebral artery ischemic stroke. His National Institutes of Health Stroke Scale (NIHSS) score was 15 due to significant right hemiparesis and expressive aphasia. The mechanism of his stroke was thought to be cardioembolic in nature due to his history of atrial fibrillation without anticoagulation.

While in the acute stroke unit, pulse oximetry showed significant oxygen desaturation with a nadir of 82% and a sawtooth pattern to the desaturations, suggestive of obstructive sleep apnea (OSA). Although the patient had expressive aphasia, he was able to write more fluently and consistently and provided written responses to assessments. His Epworth Sleepiness Scale score was 9/24 and his STOP-BANG score was 6/8, indicating a high risk for OSA. An in-laboratory split-night polysomnogram (first half diagnostic, second half therapeutic) was performed.

During the diagnostic portion, technicians recorded a sleep efficiency of 58% (normal >80%) with 5% rapid eye movement (REM) sleep (normal 15% to 25%), along with multiple obstructive events with an apnea-hypopnea index score of 51.2 events per hour (normal, <5/hour; severe, >30/hour). Oxygenation nadir was 78%, and oxygenation was below 88% for 20% of the entire sleep time (normal >95%).

During the therapeutic portion, he was fitted with a nasal mask and tested on continuous positive airway pressure (CPAP) settings of 5 cm H_2O to 15 cm H_2O. Higher pressures were associated with air pressure intolerance and persistent obstructive events. He was then switched to bilevel PAP therapy, and a setting of inspiratory PAP of 16 cm H_2O and an expiratory PAP of 12 cm H_2O best treated the patient's OSA. He was placed on bilevel PAP therapy at 16/12 cm H_2O and remained fully adherent (>4 hours of usage per night) for over 6 months. He continued to see a sleep medicine specialist to ensure adherence and efficacy of his treatment.

At his 8-month follow-up appointment with his stroke neurologist, he reported increased energy and improved daytime function. His NIHSS score was now 6 (compared with 15). He had not sustained a recurrent stroke, remained adherent to his stroke prevention medications, and was motivated to continue using PAP therapy.

COMMENT

This patient's presentation highlights the advantages and benefits of early recognition and treatment of OSA in people with acute stroke. With a multidisciplinary approach involving his stroke neurologist, his underlying diagnosis of OSA was identified as a modifiable vascular risk factor and appropriately treated to maximize his chances of remaining stroke-free.

score of 15 to 30 events/hour) showed lower apnea-hypopnea index scores in the therapy group compared with the control group (14.3 versus 19.5, P <0.05), with an overall improvement in subjective scales such as the Stanford Sleepiness Scale, the Pittsburgh Sleep Quality Index, and the Barthel Index of functioning in the therapy group.[30] Positional therapy using a supine avoidance pillow in patients with stroke and OSA showed a significant decrease in the apnea-hypopnea index score (19.5% reduction) while using the pillow; however, this was a small study with only 18 subjects and this technique challenges those with physical limitations (eg, back pain, hemiparesis).[31] Other therapies including mandibular advancement devices and upper airway surgeries, including hypoglossal nerve stimulation, have not been adequately studied in people with stroke.

Other Sleep Disturbances in Stroke

In addition to OSA, any cause of sleep disruption, including insomnia, shift work sleep-wake disorder, periodic limb movement disorder, or restless legs syndrome (RLS), have been linked to increased risk of cardiovascular and cerebrovascular events, as shown in FIGURE 10-1.[32] Impaired cardiovascular restoration, through a reduction in cardioprotective stable non–rapid eye movement (non-REM) sleep, and derangement of normal autonomic and sympathetic nervous system activation are thought to be the main mechanisms that increase the risk of

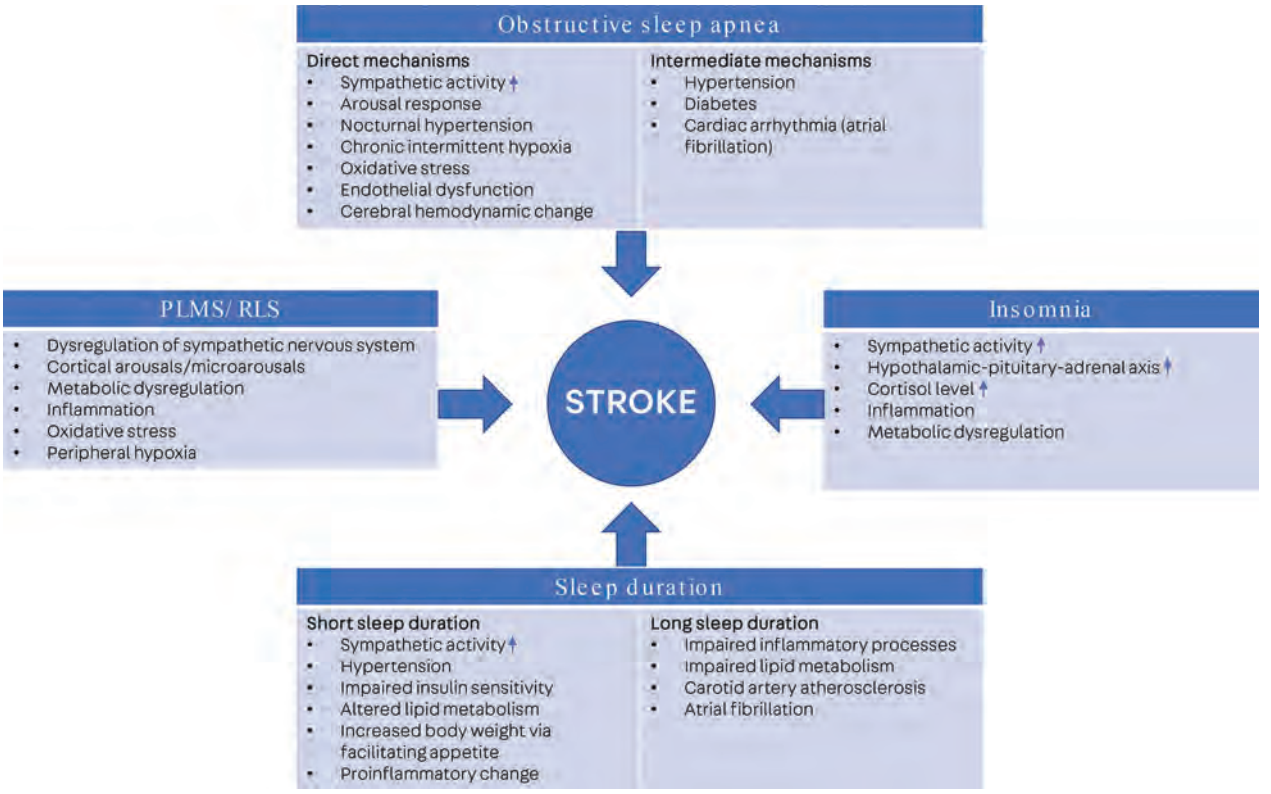

FIGURE 10-1

Mechanisms of sleep disturbances contributing to the development of stroke.

PLMS = periodic limb movements of sleep; RLS = restless legs syndrome.

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cardiovascular and cerebrovascular events. Sleep duration (long and short) also seems to play a role in the propagation of metabolic and cardiovascular disease. Long sleep duration is associated with diabetes and coronary heart disease, while short sleep duration is associated with diabetes, hypertension, and coronary heart disease.[33]

The American Heart Association recommends OSA screening with a thorough history to assess for suggestive symptoms (ie, snoring, gasping or choking for air during sleep, insomnia, and daytime hypersomnia), a complete physical examination with specific notation of the body mass index and upper airway anatomy, and implementation of practical questionnaires, such as the STOP-BANG questionnaire, Berlin Questionnaire, or the Epworth Sleepiness Scale.[34-36] Diagnostic testing for OSA should be pursued if the clinical suspicion is high. For further information on OSA, please refer to the article "Obstructive Sleep Apnea," by Karin G. Johnson, MD, FAAN, FAASM,[37] in this issue of *Continuum*. Further studies are needed to better clarify the relationship between stroke pathogenesis and OSA and better identify OSA treatment options that work best in people with stroke.

ALZHEIMER DISEASE AND OTHER COGNITIVE DISORDERS

Sleep plays an important role in disease prevention and the maintenance, regulation, and restoration of both physical and mental health. Acute and chronic sleep deprivation have been linked with neurocognitive dysfunction. In a study of 12 undergraduate students, sleep deprivation for a 24-hour period led to significant impairments in basic cognitive processes including attention, working memory, and executive functioning.[38] Chronic sleep deprivation has been associated with an increased risk of dementia. An analysis of data from 7959 participants of the Whitehall II study showed that subjects between 50 and 60 years old who slept 6 hours or less per night, compared with those who slept 7 hours or more per night, had a 30% increased risk of dementia, independent of socioeconomic, behavioral, cardiometabolic, and mental health factors.[39]

A bidirectional relationship between disturbed sleep and Alzheimer disease has been shown in animal and human studies of brain accumulation of amyloid-β (Aβ) and tau proteins (**FIGURE 10-2**[40]). These studies show that Aβ pathology correlates with the onset of sleep disturbances as early as 15 to 20 years before cognitive symptoms manifest, suggesting that sleep disruption may be a prodromal biomarker for the development of Alzheimer disease. Further aggregation and decreased glymphatic clearance of Aβ proteins correlates with decreased non-REM slow-wave sleep, decreased REM sleep, increased periods of wakefulness, circadian rhythm derangement (predominantly irregular sleep-wake rhythms), and continued progression of Alzheimer disease over time.[40,41] Several studies in humans suggest that neuronal degeneration of the suprachiasmatic nucleus, specifically neurons that express vasopressin and vasoactive intestinal peptide, lies at the root of the circadian dysfunction in Alzheimer disease. Further, multiple polymorphisms in the "clock genes" have been associated with an increased risk of Alzheimer disease, most notably the *BMAL1* gene.[42] Interestingly, the relationship between Alzheimer disease and OSA is directly moderated by apolipoprotein E (*APOE*) ε4 status and body mass index, with cognitive decline being more rapid in *APOE* ε4 allele carriers and those with higher body mass index.[43]

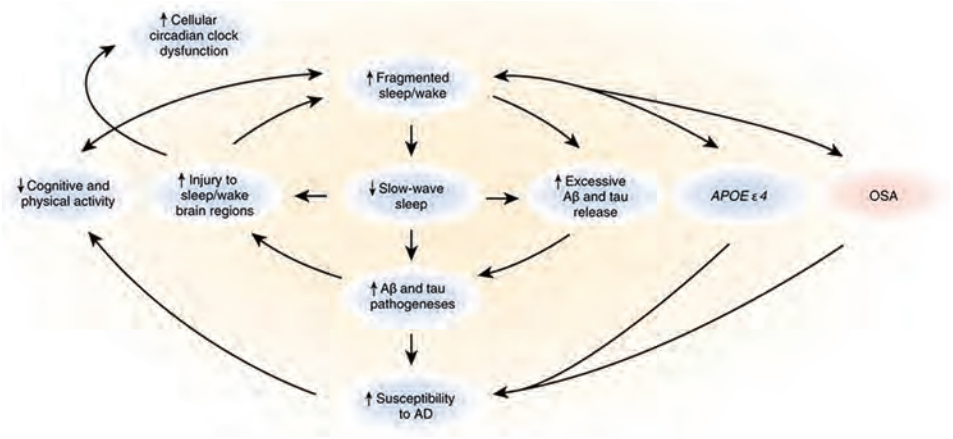

FIGURE 10-2

Interactions between sleep and Alzheimer disease (AD). The bidirectional relationships between amyloid-β (Aβ) and tau proteins and the sleep-wake cycle and the interrelationships and positive feedback loops between sleep, Aβ and tau proteins, AD, and related factors are shown.

APOE = apolipoprotein E gene; OSA = obstructive sleep apnea.

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Given the potential causal association between sleep disturbance and Alzheimer disease, potential therapeutic strategies to treat sleep-wake and circadian dysfunction early are areas of strong investigational interest.

Melatonin supplementation has shown some sleep benefit in patients with mild cognitive impairment but exhibits mixed results in restoring diurnal rhythms and reducing amyloid plaque burden in patients with Alzheimer disease. Light therapy is a potential nonpharmacologic treatment, with preliminary studies demonstrating that timed light exposure can consolidate and improve nocturnal sleep efficiency, increase daytime wakefulness, and reduce evening agitation associated with sundowning in patients with Alzheimer disease.[44] Preliminary data also support cognitive behavioral therapy for insomnia in patients with Alzheimer disease and their caregivers.[45]

Lastly, OSA has been associated with cognitive impairment and dementia. A systematic review showed that sleep apnea was associated with a significantly increased risk for dementia, including Alzheimer disease (hazard ratio 1.28; 95% confidence interval 1.16 to 1.41), dementia associated with Parkinson disease (hazard ratio 1.54; 95% confidence interval 1.30 to 1.84), and dementia with Lewy bodies (hazard ratio 2.06; 95% confidence interval 1.45 to 2.91), but not for vascular dementia.[46] CPAP has been shown to exert protective effects on mild cognitive impairment and Alzheimer disease incidence, including delayed age at onset of mild cognitive impairment, reduced mild cognitive impairment or Alzheimer disease incidence, and a 10-year delay of decline in cognitive function and progression to Alzheimer disease.[47]

PARKINSON DISEASE

Common sleep problems in Parkinson disease include insomnia, excessive daytime sleepiness, OSA, RLS, circadian rhythm sleep-wake disorders, and REM sleep behavior disorder. The prevalence of sleep disorders is as high as 40% in

people with Parkinson disease, but 30% of these individuals fail to report these symptoms to their neurologists.[48] Sleep-related symptoms are among the most commonly underrecognized nonmotor symptoms and are often debilitating for people with Parkinson disease.

Insomnia is thought to be the most common sleep disorder in Parkinson disease with a prevalence varying from 30% to 80%, with higher insomnia prevalence with Parkinson disease progression.[49] Insomnia in Parkinson disease is complex and usually multifactorial, stemming from depression, nocturnal Parkinson disease symptoms (eg, dystonia, pain, nocturia, hypokinesia), and medication side effects from the use of dopaminergic agents. Neurodegeneration can also affect the sleep-wake regulatory centers. Chronic insomnia and poor sleep quality are associated with lower health-related quality of life and worsening symptoms such as gait and balance difficulties, autonomic instability, and even hallucinations or worsening cognition.[50] The Parkinson Disease Sleep Scale is a questionnaire used to screen for insomnia in people with Parkinson disease.[51] Treatment of the nocturnal motor symptoms of Parkinson disease with controlled-release carbidopa/levodopa or dopamine agonists, like the transdermal rotigotine patch, can help mitigate insomnia. Eszopiclone and melatonin,[48] along with nonpharmacologic options including light therapy,[49] are potentially useful for the treatment of insomnia in people with Parkinson disease.

Excessive daytime sleepiness can also be common in people with Parkinson disease, manifesting as sleep attacks induced by dopaminergic drugs and hypersomnia caused by degeneration of the hypothalamic and brainstem nuclei that are responsible for wakefulness. Evaluation for comorbid sleep disorders such as RLS, OSA, and REM sleep behavior disorder as clinically indicated is important. The Epworth Sleepiness Scale can gauge excessive daytime sleepiness and treatment response. Modafinil has shown some utility in helping excessive daytime sleepiness in patients with Parkinson disease, but larger studies are needed.[48] Studies using caffeine to manage excessive daytime sleepiness in patients with Parkinson disease are inconclusive with insufficient evidence to show therapeutic benefit.

OSA can occur in up to 60% of people with Parkinson disease, with upper airway obstruction from laryngopharyngeal motor dysfunction as a possible mechanistic cause. Polysomnography or home sleep apnea testing can be used as clinically indicated to diagnose OSA.[52] Anxiety, depression, cognition, and overall sleep quality have been shown to improve after 12 months of CPAP use in patients with OSA and Parkinson disease.[53] Interestingly, carbidopa/levodopa has also been shown to improve OSA in patients with Parkinson disease.[52]

RLS is more prevalent in patients with Parkinson disease following treatment with antiparkinsonian therapy and in patients with more advanced Parkinson disease including severe limb parkinsonism, dysautonomia, or poor nutritional status.[54] This observation suggests a common dopaminergic pathway between Parkinson disease and RLS. It is important to differentiate the clinical features of RLS, defined in the *International Classification of Sleep Disorders*, from other Parkinson disease–related symptoms including limb stiffness, dystonia, and other pain syndromes.[54] RLS treatment options include iron supplementation if ferritin levels are less than 75 µg/L, gabapentin enacarbil, and pregabalin. Current clinical consensus is to limit the use of dopaminergic agents, even in people with Parkinson disease, to prevent augmentation (eg, occurrence of RLS symptoms earlier in the day, RLS symptoms affecting the trunk or upper extremities, or both).[55]

KEY POINTS

- The Whitehall II study showed that subjects between 50 and 60 years old who slept 6 hours or less per night, compared with those who slept 7 hours or more per night, had a 30% increased risk of dementia, independent of socioeconomic, behavioral, cardiometabolic, and mental health factors.
- Irregular sleep-wake rhythms and circadian rhythm misalignment may precede cognitive decline and the onset of Alzheimer disease by decades.
- Decreased slow-wave sleep and rapid eye movement (REM) sleep has been associated with abnormal brain accumulation of amyloid-β and tau proteins.
- The relationship between Alzheimer disease and obstructive sleep apnea is directly moderated by apolipoprotein E (*APOE*) ε4 status and body mass index, with cognitive decline being more rapid in *APOE* ε4 allele carriers and those with higher body mass index.
- Light therapy is a potential nonpharmacologic treatment for sleep disturbance in the setting of Alzheimer disease, with preliminary studies demonstrating that timed light exposure can consolidate and improve nocturnal sleep efficiency, increase daytime wakefulness, and reduce evening agitation associated with sundowning.

Lastly, REM sleep behavior disorder (RBD) incidence is much higher in people with Parkinson disease than in the general population (23.6% versus 3.4%).[56] Comorbid RBD with Parkinson disease confers a higher risk of severe motor dysfunction, hallucinations, cognitive impairment, and dysautonomia.[56]

Growing literature shows that idiopathic RBD is a strong prodromal marker of α-synucleinopathies, including Parkinson disease, dementia with Lewy bodies, and multiple system atrophy, with phenoconversion rates of 6.3% per year and 73.5% within 12 years.[57]

The RBD Screening Questionnaire can screen for RBD and a clinical history of sleep-related vocalizations, complex motor behavior occurring during dream mentation (or both), and a polysomnogram showing REM sleep without atonia can confirm the diagnosis.[57] RBD management includes safety counseling, withdrawing medications that may exacerbate RBD (including serotonergic antidepressants, except bupropion), and diagnosing and treating comorbid OSA when present. Pharmacologic treatment with melatonin or clonazepam for injury prevention may be considered in specific situations, although neither medication is considered a level 1 recommendation (strong evidence).[58] For further information about RBD, refer to the article "REM Sleep Behavior Disorder and Other REM Parasomnias," by Roneil Malkani, MD, MS,[59] in this issue of *Continuum*.

MULTIPLE SCLEROSIS

Sleep disorders are reportedly 4 times more prevalent in people with multiple sclerosis (MS) as compared with the general population. The most frequent primary sleep disorders include sleep-disordered breathing, insomnia, RLS, and narcolepsy.[60]

It is often difficult to differentiate MS-related fatigue (low energy) and excessive daytime sleepiness (falling asleep) associated with comorbid sleep disorders, which may contribute to secondary fatigue in people with MS (FIGURE 10-3).[61]

Primary fatigue is related to the underlying demyelinating disease process, with possible pathophysiologic mechanisms including brain inflammation and structural changes, cytokine accumulation, autonomic dysfunction, and dysregulation of the hypothalamic-pituitary neuroendocrine pathways. Secondary fatigue is due to complications of MS including mood disorders, sleep disorders, inactivity, and side effects from disease-modifying therapies for MS.[62] Fatigue is the leading cause of decreased quality of life and affects up to 90% of people with MS.[63] Nonpharmacologic approaches to MS-related fatigue include exercise, scheduled napping, and particular attention to good sleep hygiene. Pharmacologic therapies for MS-related fatigue including amantadine, modafinil, and armodafinil are mostly anecdotal, with studies showing modest efficacy on fatigue and cognitive endpoints.[64]

Up to 40% of people with MS may experience insomnia, with most arousals due to chronic pain, nocturia from a neurogenic bladder, spasticity, and comorbid depression and anxiety. Obstructive sleep apnea can also cause insomnia in people with MS, with increased prevalence thought to be related to demyelinating lesions within the brainstem sensory and motor areas that affect respiratory drive. People with MS are at risk for both obstructive and central sleep apnea, with the latter more commonly seen in those with upper spinal cord involvement.[64] PAP therapy remains the consensus best treatment.

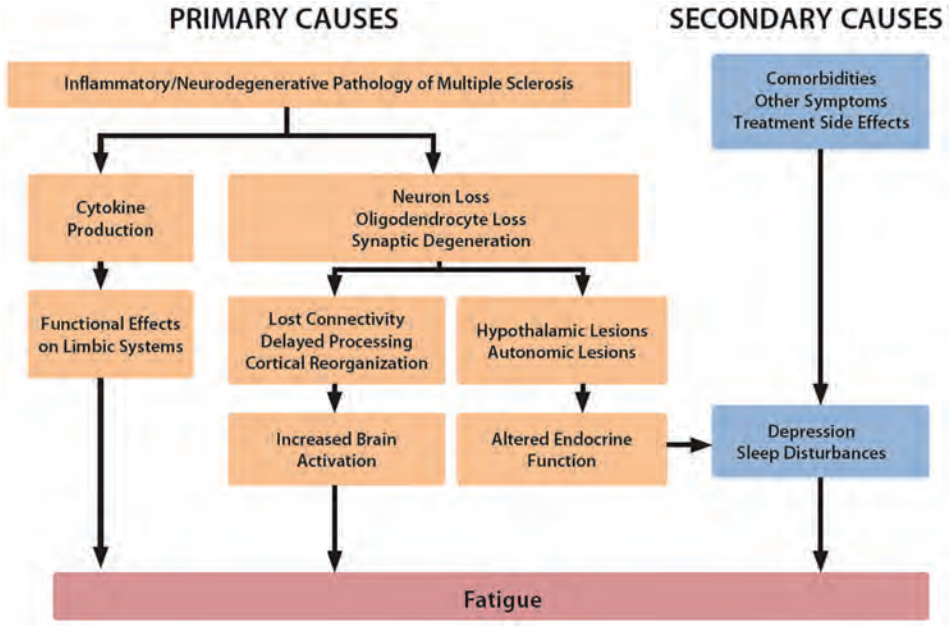

FIGURE 10-3

Fatigue in patients with multiple sclerosis.

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KEY POINTS

- **REM sleep behavior disorder is common in patients with Parkinson disease and is now considered a prodromal risk factor for the development of α-synucleinopathies including Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.**
- **Fatigue is the leading cause of decreased quality of life and affects up to 90% of patients with multiple sclerosis.**
- **Hypothalamic lesions on MRI can correlate with narcolepsy symptoms in people with multiple sclerosis and neuromyelitis optica spectrum disorder.**

RLS is 3 times more prevalent in people with MS than in the general population, potentially caused by downstream derangement of the dopaminergic pathways to the spinal cord. Other RLS risk factors include the use of dopamine-blocking antipsychotic agents, antidepressants, and antiemetics. No MS-specific treatment studies exist for RLS, but usual management interventions including checking ferritin levels and treating when ferritin levels are less than 75 μg/L with iron supplementation and consideration of initiating medications like gabapentin, carbamazepine, and pregabalin are reasonable.

Hypothalamic lesions on MRI can correlate with narcolepsy symptoms in people with MS and neuromyelitis optica spectrum disorder. In fact, the International Revised Criteria for neuromyelitis optica spectrum disorder include narcolepsy as a core clinical feature.[65]

Increased awareness, screening, and treatment of common sleep problems may help optimize function and quality of life for people with MS.

NEUROMUSCULAR DISORDERS

Sleep disturbance is common in people with neuromuscular disease and leads to significant morbidity. The underlying problems are progressive respiratory and diaphragmatic weakness, particularly in patients with amyotrophic lateral sclerosis (ALS), myotonic dystrophy types 1 and 2, and Pompe disease (acid maltase deficiency syndrome). This weakness leads to significant hypoventilation and nocturnal hypoxemia, particularly in REM sleep. People with ALS who develop bulbar weakness have higher incidences of OSA due to upper airway collapse and, less commonly, central sleep apnea. A study of 73 people with ALS compared with 20 controls found that among the people with

ALS, OSA was present in 67%, sleep-related hypoxemia was observed in 13.7%, and 5.4% had central sleep apnea syndrome.[66]

Patients with late-stage myotonic dystrophy display more central events with a Cheyne-Stokes breathing pattern, consisting of oscillations of central apneas and hyperpneas in a crescendo-decrescendo pattern. Progressive hypoventilation leads to blunted responses to hypoxemia and increased carbon dioxide levels, prompting compensatory mechanisms to retain bicarbonate renally.

All people with neuromuscular disorders at risk for ventilatory insufficiency should undergo pulmonary function testing; red flags for impending impaired breathing include a forced expiratory volume in 1 second less than or equal to 40% predicted, forced vital capacity less than 1.5 liters, a greater than 25% reduction in seated-to-supine vital capacity, and a significant reduction from baseline in maximal inspiratory pressure, maximal expiratory pressure, or sniff nasal pressure, with reference ranges dependent on sex, body mass index, and age.[67] In-laboratory overnight polysomnography with noninvasive carbon dioxide monitoring (eg, transcutaneous carbon dioxide monitors) is considered the gold standard diagnostic test to confirm sleep-related hypoventilation in people with neuromuscular and chest wall disorders; alternatively, treatment may be initiated empirically with settings adjusted based on response and arterial blood gas measurements.

Multiple retrospective studies and one randomized trial demonstrated that noninvasive ventilation prolongs survival in patients with ALS. Recent work also suggests that effects on life expectancy are stronger when noninvasive ventilation is started early (ie, in patients with only mild forced vital capacity reduction).[68-70]

EPILEPSY

Sleep and epilepsy share a bidirectional relationship. Estimates report that approximately one-third of focal seizures begin in sleep and are more likely to evolve into bilateral tonic-clonic seizures than seizures that occur during wakefulness. Sleep-related seizures more commonly occur in the "lighter" stages of non-REM sleep (N1, N2), with REM sleep being protective.[71] The most common sleep-related epilepsies include extratemporal epilepsy (eg, frontal lobe epilepsy or sleep-related hypermotor epilepsy), Landau-Kleffner syndrome (onset around age 2 to 8 years, associated with acquired aphasia, and characteristic bilateral posterior spike-and-wave discharges in N3 sleep), and childhood epilepsy with centrotemporal spikes (formerly benign childhood epilepsy with centrotemporal spikes or benign Rolandic epilepsy). Juvenile myoclonic epilepsy seizures occur shortly after awakening and present on EEG as generalized atypical spike-and-wave or polyspike-and-wave discharges.[71]

Sleep deprivation has been shown to increase seizure frequency.[72] Therefore, screening people with epilepsy for sleep concerns is important. In a study of 63 people with epilepsy, 71% had OSA, while others had chronic insomnia, insufficient sleep syndrome, or narcolepsy.[73] Insomnia and daytime hypersomnia are common in people with epilepsy; these symptoms may be related to adverse effects of antiseizure medications, comorbid sleep disorders, or both. Nasal CPAP therapy in people with seizures and comorbid OSA is associated with decreased seizure frequency and improved daytime alertness and quality of life.[74]

Chronic insomnia is also frequent in people with epilepsy, with prevalence rates around 50%. Lamotrigine can reduce slow-wave sleep and cause insomnia.[75] First line treatment for chronic insomnia in adults is cognitive behavioral therapy. Sedative-hypnotics should be avoided when possible in patients with epilepsy due to potential drug-drug interactions and preexisting risk of daytime hypersomnia related to antiseizure medications, most notably high-dose levetiracetam, valproate and its derivatives, benzodiazepines, and phenobarbital.[76]

Evidence demonstrates a strong association between sleep and the risk of sudden unexpected death in epilepsy. Estimates show that 40% to 60% of deaths due to sudden unexpected death in epilepsy are sleep-related, with direct causal mechanisms still unclear.[77]

Video-EEG polysomnography with special seizure protocols (such as the addition of frontal and temporal EEG leads) can further elucidate the presence and type of seizures and evaluate for suspected comorbid sleep disorders. A full-montage EEG in conjunction with the polysomnogram can better localize the seizure focus.

Neurostimulation with a vagus nerve stimulator has shown promise in reducing seizure frequency and improving daytime alertness, but vagus nerve stimulation may also induce OSA and stridor (sleep and awake states, respectively).[78] Epilepsy surgery has been shown to improve sleep parameters.[79]

HEADACHE SYNDROMES

Insomnia is the most common sleep disorder among people with migraine. Worsening migraine frequency has been correlated with poor sleep quality, indicated by higher Pittsburg Sleep Quality Index scores.[80] Sleep deprivation can trigger migraine attacks, while sleep has been shown to relieve migraine pain. The proposed mechanism that ties migraine and sleep so intimately is based on the trigeminal pain-signaling network and simultaneous activation of the hypothalamic and orexin (hypocretin) systems. Cognitive behavioral therapy for insomnia has been shown to successfully improve sleep and convert chronic migraine into episodic migraine.[81] After 6 weeks of single-component cognitive behavioral therapy for insomnia focusing on mostly behavioral modification techniques (eg, maintaining a consistent sleep schedule, avoiding naps), 48.5% of the participants reverted to episodic migraine from chronic migraine.[82]

Untreated OSA can also trigger migraine. In a retrospective chart review of 82 patients with headache, 52 individuals (63%) had OSA, with increasing age, female sex, and chronic migraine without aura being predictive of the presence of OSA. Within the OSA group, 82% were adherent to CPAP therapy and more likely to show improvement in their headaches than the CPAP-intolerant group.[83] Based on this study, people with headache should be screened for OSA and encouraged to use CPAP therapy when appropriate, emphasizing the likelihood of more headache-free days.

Hypnic headache is a rare headache syndrome that occurs exclusively during sleep, typically at the same time every night. It is otherwise termed *alarm clock headache* and is considered a primary headache type by the *International Classification of Headache Disorders*, *Third Edition*.[84] Hypnic headache usually occurs after 50 years old, at least 15 times per month during sleep, and lasts more than 15 minutes after awakening. Although hypnic headache can be difficult to treat, studies have shown improvement in pain with the use of caffeine for acute

KEY POINTS

- Patients with neuromuscular disease are at high risk for both obstructive and central sleep apnea.
- People with neuromuscular or chest wall disorders may undergo in-laboratory polysomnography with transcutaneous carbon dioxide monitoring to confirm sleep-related hypoventilation and hypercapnia, or they may be empirically treated with settings adjusted based on response and arterial blood gas measurements.
- Sleep-related seizures more commonly occur in the "lighter" stages of non-REM sleep (N1, N2), with REM sleep being protective.
- Sleep disruption has been shown to increase seizure frequency.
- Vagus nerve stimulation therapy may induce obstructive sleep apnea in patients, so careful preimplantation and postimplantation obstructive sleep apnea screening is important.
- Sleep apnea should be screened and treated appropriately in patients with headaches.
- There was a dramatic increase in sleep disorders during the COVID-19 pandemic, including insomnia, daytime hypersomnia, sleep-disordered breathing, and REM sleep behavior disorder.

treatment and lithium, indomethacin, and melatonin for prophylactic treatment.[85]

CONCUSSION AND TRAUMATIC BRAIN INJURY

Estimates report that 2.5 million Americans seek medical care for traumatic brain injury (TBI) each year. The most common complaint after TBI is insomnia, with a prevalence of around 29%, twice the rate of the general population.[81] Diffuse axonal injury within the sleep regulation system and injury to the hypothalamus, brainstem, and reticular activating system are some of the proposed mechanisms of sleep disorders after TBI.[86] Insomnia can develop in the acute (0 to 7 days), subacute (8 to 90 days), and chronic (after 90 days) phases after TBI and is reported to be one of the most troubling problems, along with headache and cognitive issues.

In the multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, which included 2022 participants, 43.3% reported insomnia at 2 weeks, which decreased to 27.8% at the 12-month follow-up. Among study participants, the majority (61.1%) reported mild insomnia, while 7.4% experienced severe insomnia. Women and those with a prior history of TBI or psychiatric disorders are at higher risk for severe persistent insomnia.[82] Cognitive behavioral therapy for insomnia remains the mainstay of treatment, but medications including ramelteon, zopiclone, and lorazepam have shown improvement in insomnia with no significant cognitive adverse effects. Nonpharmacologic treatments, including acupuncture, also show promise for the treatment of insomnia in this population.[87] Studies on veterans with insomnia due to posttraumatic stress disorder and TBI showed that prazosin, a selective α_1-receptor antagonist, improves sleep consolidation.[88] The use of melatonin in people with TBI has shown varying results and clinical studies in humans remain scarce.[89] More studies are needed to elucidate viable treatment options for people with TBI who have insomnia.

POST-COVID-19 SYNDROME

Sleep issues have increased during the COVID-19 pandemic and may be related to neuroinflammation within the central nervous system. A recent systematic review reported sleep concerns in 35.7% of the pooled global cohort (prior rate, 15%), with 74.8% of those infected by COVID-19 reporting sleep difficulties.[90] The rates correlate with increases in mental health concerns, with reported rates of mood disorders nearly doubling (37% in April 2020, compared with 23% from 2017 to 2019).[91] This suggests a bidirectional relationship between sleep and psychiatric comorbidities.

The prolonged disruption of normal daily activities (eg, social isolation, limited daylight exposure) and increased stress during the pandemic led to what has been termed *coronasomnia*, consisting of insufficient sleep, poor sleep quality, and sleep-wake circadian misalignment associated with physical and emotional morbidity due to COVID-19.[92] The International COVID-19 Sleep Study found an increase in insomnia, nightmares, OSA, fatigue, hypersomnia, and even RBD related to COVID-19. Weekly dream enactment behavior was 2.9 times higher in individuals who were positive for COVID-19, with the frequency of dream enactment behavior correlating to the severity of COVID-19 infection. Patients who were young, male, had a history of tobacco or alcohol use, and those with mood disorders or a history of posttraumatic stress disorder were at increased

risk of RBD in the setting of COVID-19.[93] It is unclear whether COVID-19–related RBD has similar implications for future neurodegeneration as idiopathic RBD.

Future studies are needed to evaluate patients with COVID-19 for treatment options and diagnostic strategies for associated sleep disorders. Focusing on increasing sleep quality through good sleep hygiene measures and cognitive behavioral therapy for insomnia will likely be incorporated into rehabilitation plans for patients with COVID-19.

CONCLUSION

A clear bidirectional relationship exists between sleep and various neurologic disorders. Disturbed sleep negatively impacts outcomes in neurologic disease and may also be a precursor to neurodegenerative disease states and dementia. Sleep apnea is an independent risk factor for stroke, worsens seizure frequency in people with epilepsy, and increases headache impact in those with migraine. Screening for sleep disorders and referring patients when sleep disruption is identified may improve patient outcomes and allow for comprehensive care in people with neurologic disease.

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Sleep Disorders in Childhood

By Althea Robinson Shelton, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **This article provides a comprehensive review of pediatric sleep disorders including the clinical features, diagnosis, and treatment of sleep-disordered breathing, insomnia, parasomnias, restless sleep disorder, restless legs syndrome, narcolepsy in childhood, and Kleine-Levin syndrome.**

LATEST DEVELOPMENTS: **Our understanding of pediatric sleep pathophysiology continues to evolve, and diagnostic and treatment modalities have expanded. A low-sodium oxybate formulation was approved in July 2020 in the United States to treat cataplexy and excessive daytime sleepiness in patients 7 years old and older with narcolepsy. A validated pediatric hypersomnolence survey for pediatric narcolepsy and idiopathic hypersomnia with high sensitivity, specificity, and interrater reliability is now available.**

ESSENTIAL POINTS: **The clinical presentation, diagnostics, and treatment of children with sleep disorders differ from those of adults. Untreated sleep disorders in childhood can lead to adverse physical and psychological consequences in adults. Correctly diagnosing and treating sleep disorders in youth can prevent a significant burden of disease in adulthood.**

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The institution of Dr. Shelton has received research support from Harmony Biosciences.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Shelton discusses the unlabeled/investigational use of clonazepam, clonidine, cyproheptadine, daridorexant, doxepin, gabapentin, guanfacine, hydroxyzine, lemborexant, mirtazapine, pregabalin, ramelteon, suvorexant, tasimelteon, and trazodone for the treatment of insomnia; lithium for the treatment of Kleine-Levin syndrome; amphetamine derivatives, armodafinil, clomipramine, methylphenidate, modafinil, pitolisant, and venlafaxine for the treatment of narcolepsy; and clonazepam for the treatment of parasomnias, none of which are approved by the US Food and Drug Administration (FDA).

INTRODUCTION

The regulation of sleep and wakefulness is a crucial function of the brain. Sleep disorders in children and adolescents are common and often more prevalent in children with neurodevelopmental disorders. Untreated sleep disorders may exacerbate neurologic conditions, behavior problems, and mood disorders. If sleep disorders go unrecognized in childhood, they may lead to undesired health sequelae in adulthood. Knowledge of the clinical presentations of common sleep disorders will help neurologists determine when to refer patients to a trained sleep specialist. In this article, normal sleep along with common pediatric disorders and pediatric sleep conditions such as sleep-disordered breathing, insomnia, parasomnias, restless sleep disorder, and narcolepsy are reviewed.

NORMAL SLEEP

Circadian rhythms are not fully developed at birth; thus, sleep is as likely during the day as it is at night. A typical full-term infant sleeps 16 to 18 hours per day.[1] However, the longest bouts of sleep last 2.5 to 4 hours, with 1 to 3 hours of

KEY POINTS

- The characteristic sleep change in adolescence is the natural tendency to delay sleep onset and wake times due to changes in circadian rhythm, largely driven by the release of melatonin later in the night.
- Lack of N3 and rapid eye movement (REM) sleep is associated with increased insulin resistance, and shorter sleep duration is associated with higher blood pressure in childhood.

wakeful episodes interspersed. Periods of wakefulness are driven by feeding needs.[2] Around 2 to 3 months old, the circadian rhythm emerges. The short sleep-wake cycles consolidate into more extended periods of recognizable nocturnal sleep and daytime wakefulness. In a full-term infant, nighttime sleep is consolidated by 6 months old, with the longest continuous period being 6 hours. Up to five to seven brief awakenings can occur during the night, each lasting 1 to 5 minutes.[3] Daytime sleep evolves into discrete naps. Social cues, such as the timing of feeding, begin to influence sleep-wake patterns. The total daily sleep need decreases to about 13 hours by 2 years old. Daytime naps are still common at this age. Most 1- to 2-year-old children take one or two naps every day. These naps fluctuate in length and timing; however, they are usually short and occur in the mid-mornings and early afternoons. The morning nap is eliminated first, followed by the afternoon nap. Preschoolers sleep on average 11 to 12 hours, and daytime napping is slowly discontinued. School-aged children (6 to 12 years old) require 10 to 11 hours of sleep per day.[1,3] The significant change in adolescence is the natural tendency to delay sleep onset and wake times due to changes in the circadian rhythm, largely driven by the release of melatonin later in the night. Sleep requirements in adolescents range from 8.5 to 10 hours.[2]

The ultradian rhythm refers to the alternation of two distinct types of sleep: non–rapid eye movement (non-REM) sleep and REM sleep. The ultradian rhythm changes with age. In newborns, there are three recognized types of sleep: quiet sleep (analogous to non-REM), active sleep (analogous to REM), and indeterminate sleep (comprising elements of both quiet and active sleep). Sleep onset occurs through active (REM) sleep. Equal amounts of non-REM and REM sleep occur, with the sleep cycle lasting 50 to 60 minutes. By 4 to 6 months old, infants have the three definable non-REM sleep stages (N1, N2, and N3), and REM sleep decreases to 30% to 40% of total sleep. The periodicity of the REM and non-REM sleep cycles remains 50 to 60 minutes. By 6 months old, sleep onset occurs through non-REM sleep rather than REM sleep.[1,2] By 3 years old, REM sleep makes up 20% to 25% of total sleep time with the balance spent in non-REM sleep. Stage N3 sleep occurs in the first one-third of the night, and by 5 years old the sleep cycle is 90 minutes, like the adult cycle.[1] During slow-wave sleep (N3), short-term memories are consolidated into long-term memories in the neocortex. New neural connections grow and strengthen during REM sleep. It is postulated that infants have more REM sleep to aid in developing these neural pathways.[1]

Sleep plays a vital role in child development. Cognitive, emotional, and physical development is impeded by sleep disruption. Lack of N3 sleep and REM sleep is associated with increased insulin resistance.[4] Shorter sleep duration is associated with higher blood pressure in childhood.[5] Inadequate quality or quantity of sleep in children can affect daytime function during all stages of development. Infants with sleep fragmentation have been found to have lower Mental Development Index scores on the Bayley Scales of Infant Development.[6] Preschoolers with chronic insomnia have impairment in all executive function domains (ie, planning, organizing, working memory, inhibitory self-control, and emergent metacognition).[7] For school-age children, just 1 less hour of sleep per night can significantly impact emotional lability and impulsivity in school.[8] Poor sleep impacts mental health and academic performance in adolescents.[9] Given the adverse consequences of sleep disruption on childhood development, the diagnosis and treatment of sleep disorders in childhood is of the utmost importance.

SLEEP-DISORDERED BREATHING

Sleep-disordered breathing encompasses a spectrum of respiratory disorders occurring exclusively in sleep or exacerbated by sleep. It includes primary snoring, sleep-induced hypoxemia, sleep-related hypoventilation, upper airway resistance syndrome, obstructive sleep apnea (OSA), and central sleep apnea. This section focuses on OSA and central sleep apnea.

Obstructive Sleep Apnea

OSA syndrome was not characterized in children until 1976, and the clinical presentation differences between children and adults were not described until 1981.[10] Children commonly present with classic nocturnal sleep-disordered breathing symptoms such as snoring, night awakenings, respiratory pauses, and gasping; however, children with neuromuscular weakness and infants may not snore. Children with OSA may be described as "restless" and "sweaty" sleepers. They often sleep in unusual positions (eg, seated, neck hyperextended). Difficulties with attention and hyperactivity are common daytime manifestations of sleep-disordered breathing in children.

The prevalence of OSA in children is rising due to the obesity epidemic and is currently reported to range from 1% to 5.8%, with a peak between 2 and 8 years old.[11] A 2016 study of nationwide inpatient discharges for patients younger than 21 years old showed that male sex, non-Hispanic Black race, and Hispanic ethnicity were associated with an increased risk of developing OSA.[12] In addition, children with a low socioeconomic status have an increased risk of OSA, and lower socioeconomic status is associated with increased OSA severity.[13] Adults with a history of severe childhood OSA have a high risk of snoring, elevated body mass index, and lower academic achievement.[14] Certain medical and genetic conditions confer a high risk of developing OSA (TABLE 11-1).

The pathophysiology of pediatric OSA syndrome is multifactorial. Sleep causes a natural decrease in pharyngeal muscle tone. In addition, external factors such as hypertrophied tissue, craniofacial features, and fat deposits can impact the size of the upper airway. [15] These external factors are influenced by genetics

Medical and Genetic Conditions Associated With High Obstructive Sleep Apnea Risk TABLE 11-1

- Achondroplasia
- Cerebral palsy
- Craniosynostoses
- Hunter syndrome
- Muscular dystrophy
- Pierre Robin sequence
- Prader-Willi syndrome
- Sickle cell anemia
- Spinal muscular atrophy
- Trisomy 21

and the environment.[10] The combination of a "collapsible tube" during sleep and the described external factors contributes to the multifactorial pathophysiology of OSA.

The most common cause of pediatric OSA is adenotonsillar hypertrophy.[12] MRI studies of the upper airway in children have found that those with OSA syndrome have larger tonsils and adenoidal tissue than controls.[16] Adenotonsillectomy remains the consensus preferred treatment for OSA syndrome in children,[17] and its effectiveness is reported to be as high as 80%.[18] Tonsillar size does not necessarily correlate with the degree of obstruction, and some children have a degree of tonsillar hypertrophy that does not contribute to OSA syndrome development.[19] Thus, while adenotonsillar hypertrophy is a well-known cause of OSA syndrome in the pediatric population, other factors also play a role. OSA syndrome can reoccur in adolescence after resolution from adenotonsillectomy in childhood.[20]

Abnormal muscle tone, abnormal breathing during sleep, and abnormal development of oral-facial structures have reciprocal relationships.[21] OSA syndrome commonly develops in children with craniofacial abnormalities that involve hypoplasia or retropositioning of the mandible or maxilla.[21] High-arched palate, retrognathia, and midface hypoplasia also place children at a higher risk of developing OSA syndrome.[22] Upper airway obstruction and mouth breathing induce morphologic skeletal changes in the maxilla and mandible. Dentoalveolar morphology is influenced by chronic mouth breathing, resulting in a narrow maxilla, retrognathia, and a high-arched narrow palate.[23]

In addition to the anatomic influences mentioned above, neuromuscular activation plays a key role in upper airway stability and thus the development of OSA.[23] Patients with OSA syndrome do not obstruct during wakefulness, suggesting that motor dysfunction during sleep plays a role in OSA development.[19] The pressure at which airway collapse occurs, known as the critical closing pressure, can be in the positive range for children with OSA syndrome, indicating a lower threshold for airway collapse, whereas children without OSA syndrome can maintain inspiratory airflow at subatmospheric pressures.[24] The critical closing pressure correlates with the severity of OSA. Children with OSA who undergo treatment with adenotonsillectomy can continue to have elevated critical closing pressure values compared to controls.[24] This finding suggests that with changes in upper airway pressure, patients with OSA syndrome cannot maintain sufficient motor tone.[22]

Pediatric obesity is defined as a body mass index above the 95th percentile for age and sex[12] and is an independent risk factor for pediatric OSA.[25] It is estimated that OSA prevalence in children with obesity is as high as 60%.[26] In a recent meta-analysis evaluating adenotonsillectomy for OSA in children with obesity (408 patients from 11 studies), rates of persistent OSA ranged from 51% to 66% (**CASE 11-1**).[27] The severity of sleep apnea is determined by the apnea-hypopnea index (AHI), which quantifies how many times per hour a person experiences either shallow breathing (hypopnea) or cessation of breathing (apnea). The overall postoperative AHI resolution rates for children with obesity ranged from 34% to 44% compared with previous reviews of children without obesity that reported AHI resolution rates between 63% and 85%.[27]

The neurocognitive effects of untreated OSA are significant. Changes in behavior and learning often alert a caregiver to problems with their child's sleep. Understanding of the impact of sleep-disordered breathing on cognition,

behavior, and learning has grown over the last 2 decades. In a 2015 meta-analysis, sleep-disordered breathing was associated with unsatisfactory progress in school, learning problems, and poor academic performance in math, language arts, and science.[28] Multiple studies have shown a relationship between attention deficit hyperactivity disorder (ADHD) and OSA syndrome. This association was confirmed by a meta-analysis that showed a moderate relationship between ADHD and OSA syndrome. Adenotonsillectomy was associated with decreased ADHD symptoms at 2 to 13 months postsurgery.[29] Another meta-analysis conducted in 2017 evaluated neurocognitive effects in children with OSA posttonsillectomy and postadenoidectomy. Subsequent neuropsychological testing conducted within these studies found improvements in patients' executive function, attention, memory, and learning.[30] This evidence suggests that screening for sleep-disordered breathing should be included in pediatric and multidisciplinary assessments of children who present with learning difficulties.

Hypertension is a well-known cardiovascular risk factor in adults. The incidence of cardiovascular disease in adulthood may depend on whether certain risk factors in childhood, such as OSA, persist into adulthood.[31] A longitudinal cohort study following 493 children into adulthood showed that children with elevated blood pressure were at increased risk of developing hypertension as adults.[32] Multiple studies across all age ranges have shown elevated blood pressure in patients with OSA. One study demonstrated that 52% of children with severe OSA (AHI score of 10 or greater) had stage 2 hypertension.[33] Childhood OSA is an independent risk factor for adverse blood pressure outcomes.[34] Fortunately, studies have shown improvement in blood pressure once OSA in children is treated with either adenotonsillectomy or continuous positive airway pressure (CPAP) therapy.[35] Blood pressure should be regularly monitored in children and adolescents with OSA to identify those at higher risk of continued hypertension into adulthood.

Overnight polysomnography (PSG) is the gold standard test for the diagnosis of sleep-disordered breathing in children. In children, an AHI score of greater than 1 event per hour is abnormal. In addition, a pattern of obstructive hypoventilation, with 25% or more of total sleep time with hypercapnia, a partial pressure of carbon dioxide in arterial blood greater than 50 mm Hg associated with snoring, flattening of inspiratory nasal pressure waveform, or paradoxical thoracoabdominal motion is diagnostic of OSA.[16] Recent studies have classified an obstructive AHI score of 2 events per hour or more as indicative of OSA in children and adolescents.[17]

Adenotonsillectomy remains the recommended first-line OSA treatment for children.[36] In the childhood adenotonsillectomy trial, adenotonsillectomy resolved OSA in 79% of subjects, compared with resolution in only 46% of subjects who underwent watchful waiting.[17] However, the prevalence of residual OSA after adenotonsillectomy has been reported to be as high as 25% to 40%.[37] Most otherwise healthy children can have adenotonsillectomy performed as an outpatient. Recent clinical practice guidelines from the American Academy of Otolaryngology recommend that children younger than 3 years old or with severe OSA syndrome (AHI score ≥ 10 events per hour or oxygen desaturation nadir <80%) are at increased risk for postoperative complications and should be observed overnight. A repeat PSG is recommended for patients with an AHI score of 10 or more events per hour.[36] Adenotonsillectomy is successful in many patients, but residual OSA can persist after surgery, especially in those with

CASE 11-1

A 10-year-old girl presented with multiple nighttime awakenings and disruptive behavior in the classroom. Her parents reported that she snored loudly and occasionally choked and coughed in her sleep. She was described as a restless and sweaty sleeper. Her parents reported that she slept at night with her neck hyperextended. It was difficult for her to wake up in the morning. She had recently become disruptive in class and had difficulty with her schoolwork. Her physical examination was notable for obesity and enlarged tonsils. An overnight polysomnogram was ordered which showed severe obstructive sleep apnea (FIGURE 11-1A).

She was urgently referred to pediatric otolaryngology. She underwent an adenotonsillectomy. Postsurgically, her mother reported that her snoring had improved. She had soft, intermittent snoring and no longer woke up at night. However, she was still restless during sleep. During the day, she was still disruptive. Her grades had not improved. A repeat polysomnogram was obtained 4 months after surgery (FIGURE 11-1B).

Treatment options were discussed in the clinic, including a return visit to otolaryngology for a possible drug-induced sleep endoscopy, continuous positive airway pressure (CPAP) therapy, and weight management. The family decided to initiate CPAP, and they were referred to the pediatric weight management clinic.

COMMENT

This case illustrates the clinical presentation of obstructive sleep apnea, including attention deficit hyperactivity disorder–like behavior during the day. In addition, children with obesity can have obstructive sleep apnea that persists even after adenotonsillectomy, which necessitates the use of other treatment modalities.

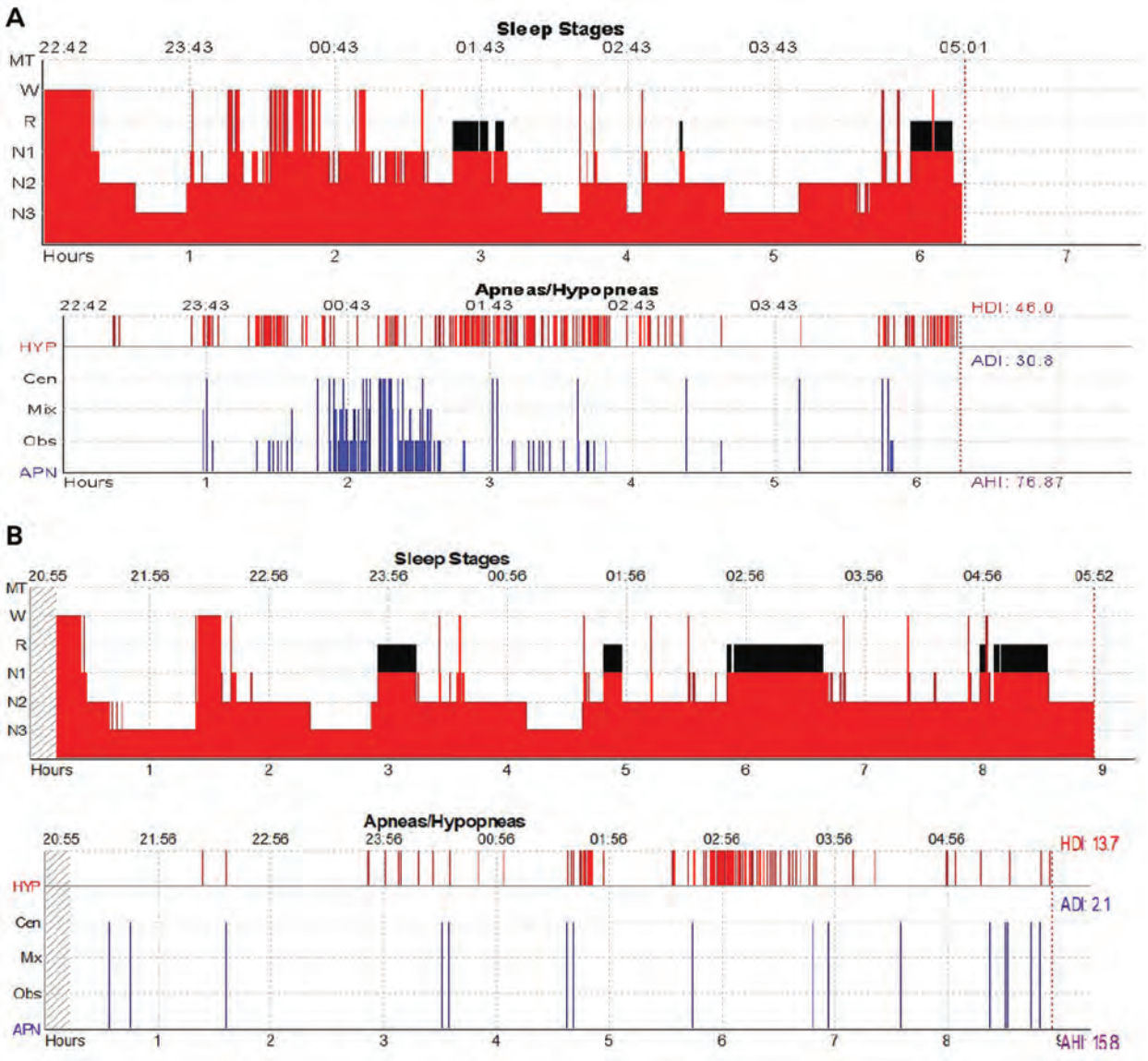

FIGURE 11-1

Polysomnograms (PSGs) for the patient in CASE 11-1. The preoperative PSG (*A*) indicates very severe obstructive sleep apnea, which is worse during rapid eye movement (REM) sleep, with associated hypoxemia and disruption in sleep architecture. The baseline apnea-hypopnea index (AHI) score is 76.8 events per hour. The oxygen saturation nadir is 77%, and the REM AHI score is 99.1 events per hour. There is limited REM sleep. When central apneas are excluded, the resulting obstructive AHI score is 69.7 events per hour. The postoperative follow-up PSG (*B*) shows improved but still severe obstructive sleep apnea, which is worse during REM and supine sleep, with associated severe hypoxemia and disruption in sleep architecture. The baseline AHI score is 15.8 events per hour. After eliminating physiologic REM-related and postarousal central events, the obstructive AHI score is 13.7 events per hour, the REM AHI score is 43.4 events per hour, the supine AHI score is 21 events per hour, and the oxygen nadir is 77%. Concurrent supine and REM sleep was recorded. The patient reported the same quality of sleep as at home.

ADI = apnea disturbace index; APN = apneas; Cen = central; HDI = hypopnea disturbance index; HYP = hypopneas; Mix = mixed; Obs = obstructive.

KEY POINTS

- Screening for sleep-disordered breathing should be included in general pediatric and multidisciplinary assessments of childhood learning difficulties.
- Children and adolescents with obstructive sleep apnea should have regular blood pressure monitoring to identify those at higher risk of continued hypertension into adulthood.
- In addition to adenotonsillectomy, surgical options for obstructive sleep apnea include lingual tonsillectomy, supraglottoplasty, posterior midline glossectomy, and palatopharyngoplasty.
- Drug-induced sleep endoscopy is a method that can help visualize the level of collapse in the upper airway while the patient is sedated, which likely replicates upper airway physiology during sleep.
- Midface hypoplasia from the long-standing pressure of the mask on growing facial structures is a possible adverse effect of positive airway pressure therapy in children. Thus, it is essential to perform regular mask fittings.

comorbidities. Children and adolescents with severe OSA, obesity, and chronic asthma, and children with neurologic, developmental, or craniofacial conditions are at high risk of residual OSA following adenotonsillectomy.[38]

Other surgical interventions for OSA in children include lingual tonsillectomy, supraglottoplasty, posterior midline glossectomy, and palatopharyngoplasty.[39] These surgeries can collectively be called *multilevel upper airway surgery*. Postadenotonsillectomy evaluation of residual OSA may include procedures to visualize the upper airway during a sleeplike state. For example, cine-MRI can be performed while the patient is sedated. During cine-MRI, repetitive MRI images are obtained while the patient is in a drug-induced sleep state. The images are merged into a "cine" or movie format which is assessed for sites of obstruction. Drug-induced sleep endoscopy facilitates visualization of the level of upper airway collapse while the patient is sedated, which is postulated to replicate the upper airway collapsibility that occurs during sleep. However, controversy exists about how well drug-induced sleep endoscopy simulates physiologic sleep. A 2019 meta-analysis examining the efficacy of upper airway surgery after adenotonsillectomy demonstrated that both drug-induced sleep endoscopy and cine-MRI–directed surgeries significantly improved designated PSG parameters. However, complete resolution of OSA was rarely observed.[40]

Positive airway pressure (PAP) is an effective treatment for children with OSA who are not candidates for adenotonsillectomy, multilevel upper airway surgery, or both, or whose caregivers decline surgery. PAP's major effects are preserving airway patency throughout the respiratory cycle while asleep and reducing breathing in the setting of increased airway resistance.[41] Commonly used PAP modes in children include CPAP, autoadjusting PAP, and bilevel PAP (BiPAP). Midface hypoplasia from the long-standing pressure of the mask on growing facial structures is a possible adverse effect of PAP therapy in children.[41] Thus, it is essential to perform regular mask fittings. Adherence to PAP therapy is a significant barrier to effective treatment. In a pediatric population, PAP adherence is usually less than 50%.[42]

Approaches to correct craniofacial abnormalities associated with OSA in children include rapid maxillary expansion and myofunctional therapy. Rapid maxillary expansion is an orthodontic procedure used to expand the hard palate in patients with maxillary constriction. It involves the placement of an appliance anchored to a patient's teeth that spans the hard palate. Patients with mandibular retroposition, a high-arched palate, or both are the best candidates for rapid maxillary expansion. A systematic review of rapid maxillary expansion use in OSA treatment showed that it decreased AHI scores by 70%.[43] Myofunctional therapy involves specific oropharyngeal exercises to improve the use of nasal breathing over mouth breathing by improving labial seal and tone.[44] A meta-analysis showed that myofunctional therapy decreased AHI scores by 50% in adults and 62% in children and concluded that it could serve as an adjunct treatment.[43] Adherence to the daily exercise schedule is a barrier to treatment with traditional myofunctional therapy.

Medical management with intranasal corticosteroids and leukotriene inhibitors such as montelukast are possible treatment options, especially for patients with mild OSA. A meta-analysis of children with mild OSA syndrome found that montelukast alone improved AHI scores by 55% and that montelukast with intranasal corticosteroids improved AHI scores by 70%.[45] For example, an AHI score of 1.5 events per hour could be normalized if improved by 50%.

Hypoglossal nerve stimulation is US Food and Drug Administration (FDA) approved for OSA treatment in appropriately selected adults.[46] Hypoglossal nerve stimulation is currently being studied in children without obesity and adolescents and young adults (ages 10 to 21 years) with trisomy 21 syndrome. A case series of 20 children and young adults with trisomy 21 syndrome and OSA treated with hypoglossal nerve stimulation showed an 85% median reduction of AHI scores and average use of 9.21 hours.[47]

Central Sleep Apnea

Central sleep apnea is another important disorder on the spectrum of sleep-disordered breathing. In children, a central apnea on PSG is defined as a reduction in airflow of at least 90% without respiratory effort that lasts more than two baseline respiratory cycles associated with any combination of the following: at least a 3% reduction in oxygen saturation, an arousal, an episode of bradycardia in infants, or a central apnea lasting 20 seconds.[48] A central apnea index (CAI) score of 1 event per hour or fewer is widely considered normal, whereas a CAI score of 5 or more events per hour is considered clinically significant.[49] Central sleep apnea is rare in healthy children. In a retrospective study reviewing PSGs of approximately 2900 pediatric patients, only 3% were found to have central sleep apnea, defined as a CAI score of 5 or more events per hour.[50] Central sleep apnea generally occurs in the setting of an underlying medical disorder[49] and can happen in the context of OSA.[51] Medical conditions commonly associated with central sleep apnea include Chiari malformation and other brainstem abnormalities, genetic disorders like Prader-Willi syndrome and trisomy 21 syndrome, hypothyroidism, chronic kidney disease, laryngomalacia, and gastroesophageal reflux.[52] Other causes of hypoventilation like congenital central hypoventilation syndrome exist. The hallmark of congenital central hypoventilation syndrome is alveolar hypoventilation.[53] Many children with central sleep apnea are asymptomatic and the finding of central sleep apnea is incidental, so patients at high risk of developing central sleep apnea should be screened. Healthy children with the finding of central sleep apnea on polysomnogram should be referred for brain MRI,[49] as the most common cause of central sleep apnea in otherwise healthy children is Chiari malformation.[50] If a specific underlying medical condition exists, testing should be directed to that medical condition.[49]

Recommended Sleep Times for Pediatric Populations[a] TABLE 11-2

Age	Recommended total sleep time (hours) per 24 hours
4 to 12 months	12 to 16
1 to 2 years	11 to 14
3 to 5 years	10 to 13
6 to 12 years	9 to 12
13 to 18 years	8 to 10

[a] Data from Paruthi S, et al, J Clin Sleep Med.[54]

KEY POINT

- Central sleep apnea is rare in healthy children. The most common cause of central sleep apnea in otherwise healthy children is Chiari malformation.

INSOMNIA

The American Academy of Sleep Medicine and the Sleep Research Society recommend the appropriate amount of sleep per 24 hours for pediatric populations to promote optimal health (TABLE 11-2).[54] The *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*) defines insomnia as a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep and results in daytime impairment.[55] The prevalence of pediatric insomnia changes with age. In preschoolers and school-age children, the prevalence ranges from 50% in some preschool populations to 15% in school-age children.[56,57] A recent study showed that the persistence of childhood insomnia into adolescence was 56%.[58]

The classification of pediatric insomnia has been combined with adult insomnia criteria and is called *chronic insomnia disorder*.[55] For more information on insomnia, refer to the article "Insomnia," by Scott Kutscher, MD, and Christine Juang, PhD, DBSM,[59] in this issue of *Continuum*. However, pediatric insomnia can still be described using the three subtypes of behavioral insomnia: sleep-onset association type, limit-setting type, and combined type. Children with sleep-onset association insomnia associate sleep onset with a certain object or person; thus, when they naturally awaken at night, they need that object or person to fall back to sleep. This subtype, commonly seen in infants and toddlers, can lead to multiple awakenings at night. Limit-setting insomnia is characterized by bedtime resistance, which may manifest as a child having multiple requests (eg, more hugs, more water) before falling asleep. Thus, sleep onset is delayed. Once asleep, they tend to stay asleep. This subtype is most often seen in preschoolers and early school-age children. The combined type of insomnia is characterized by a mix of the two subtypes described above.[55]

A latent class analysis found the existence of three possible phenotypes of childhood insomnia, distinct from the classification system described above. This system is based on specific symptoms and characteristics of insomnia together with family-related sleep history.[60] The three phenotypes described are:

- Insomnia with motor restlessness associated with difficulty falling asleep and multiple awakenings at night; this type is associated with a family and clinical history of iron deficiency anemia, growing pains, and restless legs syndrome (RLS).
- Insomnia with mainly early morning awakenings; this type is associated with a family history of mood disorders or depression and headache or migraine.
- Insomnia with high-frequency nocturnal awakenings with difficulty falling asleep; this phenotype is associated with a family and clinical history of allergies and food intolerance.[60]

It is hypothesized that the three phenotypes represent dysfunction in different neurotransmitter systems (dopaminergic, serotonergic, and histaminergic, respectively).[60] The novel aspect of this classification is that each type necessitates a different treatment approach (behavioral and possibly medical) (FIGURE 11-2). This schema represents a more personalized approach to the treatment of pediatric insomnia and thus may be more effective. Effective treatment of pediatric insomnia will decrease the detrimental effect that poor sleep has on a child's daytime functioning and mood.[61]

The pathophysiology of insomnia is undetermined. A well-accepted theory suggests that genetic predisposition and factors such as medical and psychosocial stress in association with cortical, autonomic, and somatic arousal increase sensory processing and result in insomnia.[62]

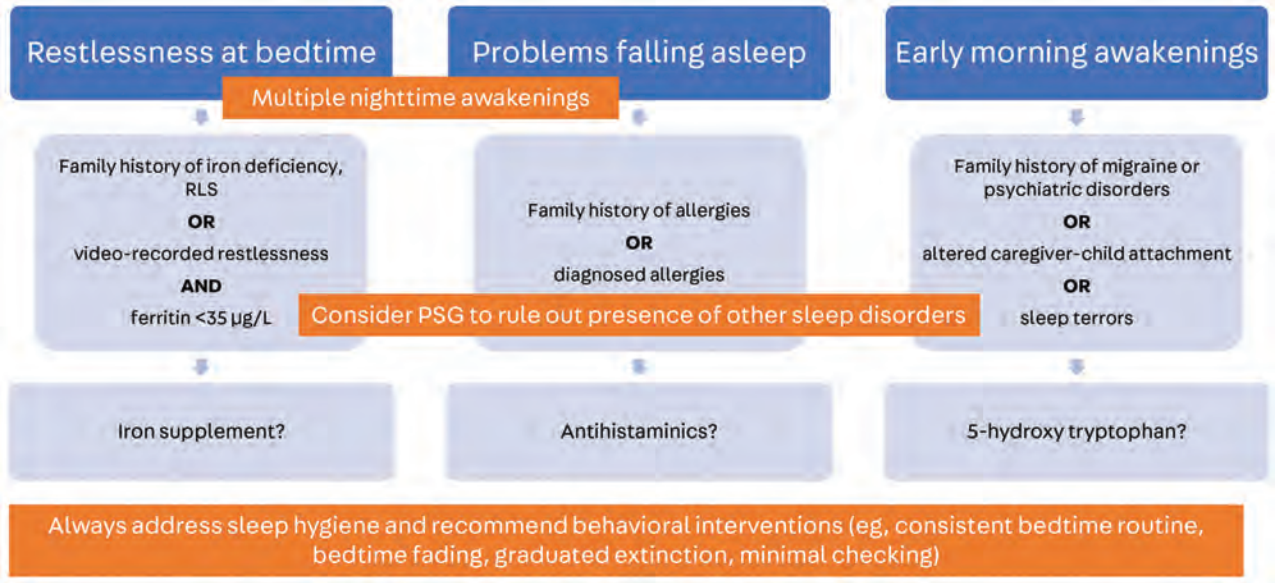

FIGURE 11-2
Phenotypes of behavioral insomnia.
PSG = polysomnography; RLS = restless legs syndrome.
Modified from Bruni O, et al, J Pediatr.[60] © 2018 Elsevier Inc.

A thorough sleep and medical history should be taken to exclude other sleep disorders as the cause of insomnia (eg, RLS may be the underlying cause of sleep-onset insomnia, OSA may cause sleep maintenance issues). PSG should be performed if OSA is suspected to contribute to insomnia. Sleep diaries or logs can provide an overview of self-reported sleep-wake patterns. The BEARS Sleep Screening Tool (**b**edtime problems, **e**xcessive daytime sleepiness, **a**wakenings during the night, **r**egularity and duration of sleep, and **s**leep-disordered breathing) may also be helpful (TABLE 11-3).[63] Actigraphy is another diagnostic tool that can provide objective evidence. An actigraph is a watchlike device, worn on the wrist, that detects physical motion and produces a signal in response to movement (acceleration). Sleep parameters are estimated from the data collected, using movement as a surrogate to estimate wakefulness.

Behavioral interventions should always be the first line in the treatment of pediatric insomnia, as they produce reliable and durable changes.[64] A meta-analysis of behavioral interventions in pediatric insomnia found moderate-level evidence that supports behavioral interventions for pediatric insomnia in young children (<4 years old).[65] In typically developing children significant effects (small to medium effect sizes) were found for sleep-onset latency, the number of night awakenings, duration of night awakenings, and sleep efficiency. No significant effects were found in two studies involving children with neurodevelopmental disorders.[65]

Behavioral therapies for childhood insomnia include extinction (unmodified and graduated), bedtime fading with positive routines, and scheduled awakenings.[61]

Unmodified extinction is commonly referred to as "crying it out." This method can be stressful to caregivers, and thus graduated extinction is often

preferred.[64] Graduated extinction steadily limits caregiver involvement in sleep onset; caregivers are instructed to ignore bedtime crying for specified periods by utilizing a fixed schedule (eg, every 5 minutes) or waiting for increasingly longer intervals (eg, 5 minutes, then 10 minutes, then 15 minutes) before checking on their child. The caregivers are instructed to minimize interactions during brief check-ins.[64] Both unmodified and gradual extinction are effective without adverse effects.[66]

Bedtime fading postpones bedtime to a time that fits the child's natural tendency. Positive routines involve caregivers developing two to four enjoyable, consistent bedtime routines that move in the direction of the bedroom, such as turning off electronics, coloring, then taking a bath, and finally reading the child's favorite book in their bedroom. When the association between positive bedtime events and falling asleep is formed, the bedtime is moved earlier by 15 minutes over consecutive nights until the bedtime goal is reached.[64]

Scheduled awakenings involve caregivers waking and typically consoling their child (eg, feeding, rocking, soothing) approximately 15 to 30 minutes before a typical spontaneous awakening. Scheduled awakenings are then faded out by regularly increasing the period between awakenings.[64] Parent education on sleep and sleep hygiene are essential in all behavioral interventions.[61]

A family's culture and socioeconomic status should be considered when initiating behavioral strategies. Most behavioral intervention research has mainly involved participants of higher socioeconomic status who are White and highly educated.[67] One study sought to address this sleep health disparity with evidence-based behavioral sleep interventions implemented in primarily Black, low-socioeconomic status, urban young children and their families.[68] Culturally sensitive and family-centered adaptations were made, and interventions were delivered in a pediatric primary care setting to expand access. Specific treatment modifications included flexibility in sleep timing personalized to the family's work schedules, collaboration among multiple family members to implement sleep routines, working within shared sleep spaces due to limited resources or family preference, and increased visual support and technology use in

TABLE 11-3

BEARS Sleep Screening Tool[a]

Sleep domain	Trigger questions for young children (2 to 5 years old)
Bedtime problems	Does your child have any problems going to bed or falling asleep?
Excessive daytime sleepiness	Does your child seem overly tired or sleepy during the day? Does your child still take naps?
Awakenings during the night	Does your child frequently awaken at night?
Regularity and duration of sleep	Does your child have a regular bedtime and wake time?
Sleep-disordered breathing	Does your child snore or have difficulty breathing at night?

[a] Data from Owens JA, Moore M, Pediatr Ann.[63]

intervention delivery. Observed outcomes included reduced sleep-onset latency, reduced duration of nocturnal awakenings, and increased nocturnal sleep time.[68]

As stated above, behavioral intervention should be the first-line treatment for insomnia in children, as no medications are approved by the FDA to treat insomnia in children or adolescents. Off-label use of medications for childhood insomnia is common. Melatonin is commonly used to treat pediatric insomnia. Multiple studies have shown that melatonin is effective in patients with typical development and patients with neurodevelopmental disorders.[69-72] Melatonin is most effective when combined with behavioral intervention and parent education. Melatonin reduces sleep-onset latency, increases total sleep time, and improves sleep quality.[73] Concerns have been raised about melatonin's effect on physical development; however, a 3-month, double-blind, placebo-controlled study evaluating the safety and efficacy of prolonged-release melatonin showed no changes in pubertal status (Tanner staging done by a physician). Pubertal status was within normal ranges with no evidence of delay in body mass index or pubertal development.[74]

Medications Used for Pediatric Insomnia[a] TABLE 11-4

Medication class	Mechanism of action	Examples	Comments
Benzodiazepines and benzodiazepine receptor agonists	Bind to central $GABA_A$ receptors	Clonazepam	Also used to control partial arousal parasomnias (night terrors, sleepwalking); schedule IV drugs
Selective histamine 2 receptor antagonists	Selective antagonism of histamine 2 receptors	Doxepin	Used for sleep maintenance insomnia
Antihistamines	Competitive antagonism of histamine 2 receptors in the central nervous system	Hydroxyzine, cyproheptadine	Has high level of parental and practitioner acceptance
α-receptor agonists	α_2-receptor agonists; decrease NE release	Clonidine, guanfacine	Also used in daytime treatment of attention deficit hyperactivity disorder; guanfacine is more selective
Atypical antidepressants	Antagonism of histamine 2 receptors	Trazodone, mirtazapine	May be used with comorbid mood disorder
Gabapentinoids	Selective N-type calcium channel antagonist	Gabapentin, pregabalin	Used for sleep maintenance insomnia
Dual orexin receptor antagonist	Bind to OX1R and OX2R receptors and inhibit the activation of the arousal system	Daridorexant, lemborexant, suvorexant	Schedule IV drugs
Synthetic melatonin receptor agonists	Agonism of melatonin MT1 and MT2 receptors	Ramelteon, tasimelteon	May be effective in some children even if melatonin was ineffective; avoid coadministration with fluvoxamine

$GABA_A$ = γ-aminobutyric acid A; IV = intravenous; MT1/MT2 = melatonin receptor 1/2; NE = norepinephrine; OX1R/OX2R = orexin (hypocretin) receptor 1/2.

[a] Data from Ekambaram V, Owens J, Child Adolesc Psychiatr Clin N Am.[75]

KEY POINTS

- Behavioral interventions should always be the first line in the treatment of pediatric insomnia.
- A family's culture and socioeconomic status should be considered when initiating behavioral strategies for the management of insomnia.
- Non-REM parasomnias such as sleepwalking, confusional arousals, and sleep terrors occur in the first third of the night.

If a medication trial is pursued, practitioners should emphasize an individualized approach. Whenever possible, medications should be chosen that will also treat a comorbidity, such as hyperactivity, epilepsy, anxiety, or a mood disorder. Commonly prescribed medication classes used to treat insomnia are listed in TABLE 11-4.[75]

PARASOMNIAS

Parasomnias are undesirable physical events or experiences during entry into sleep, within sleep, or during arousal from sleep. The *ICSD-3-TR* classifies two types of parasomnias: REM parasomnias and non-REM parasomnias.[55] This section focuses on non-REM parasomnias, which are more common in the pediatric population and are also known as *disorders of arousal*. Disorders of arousal arise from incomplete arousals during non-REM sleep, usually from deep sleep (stage N3 sleep); they include confusional arousals, sleep terrors, and sleepwalking.[55] Sleep-related eating disorder is a non-REM parasomnia but it is not classified as a disorder of arousal.[55] Non-REM parasomnias are usually benign but can lead to injury or cause meaningful sleep disruption for the child and family, with subsequent daytime sequelae.

Non-REM parasomnias occur in the first third of the night, 1 to 3 hours after falling asleep, when N3 sleep primarily occurs. The next morning there is either no recollection or only partial recollection of the event.[55] Confusional arousals occur in the absence of terror or ambulation outside of bed. Caregivers often describe children sitting up in bed with their eyes open and appearing awake but confused. The episode may be associated with agitation, crying, or moaning, and speech is sparse and slow. These events are characterized by disorientation, confusion, and grogginess. A lack of autonomic activation is typically seen, such as tachycardia, diaphoresis, and mydriasis.[55]

In contrast, sleep terrors are characterized by signs of intense fear and autonomic arousal; caregivers often describe a sudden cry or intense screaming associated with the appearance of extreme fear. Evidence of autonomic activation includes sweating, pallor, tachypnea, tachycardia, and mydriasis. During a sleep terror, children may become agitated and disoriented when a caregiver tries to console them.[55]

Sleepwalking is associated with ambulation out of bed, which can involve standing by the bed, walking, or running; sleepwalking can start as confusional arousal. Children's eyes are often open, and they may mumble or speak incoherently. Sleepwalking can involve normal routine behaviors that are inappropriate because of their timing or location, such as urinating in the wrong location, opening doors, or attempting to climb on furniture or walls during sleep. Accidents and injuries are often associated with sleepwalking because judgment is impaired.[55]

Sleep-related eating disorder consists of repeated spells of involuntary dysfunctional eating that occur after an arousal from sleep. Patients often report a lack of control with overeating and thus eat odd food combinations or even things that are not edible. Harmful health consequences (eg, diabetes, obesity) or sleep-related injurious behaviors can occur.[55]

Non-REM parasomnias predominate in childhood. They tend to arise out of N3 sleep and decrease along with the spectrum of development and into adulthood, likely because of the reduction in N3 sleep that occurs with age.[76] Between 2.5 and 6 years old, 88% of children will experience at least one

parasomnia.[77] The prevalence of sleepwalking peaks between 8 and 12 years old, with a longitudinal study finding a peak at 10 years old. This same study found that sleep terrors peak at 1.5 years old and occur in 34% of children younger than 7 years old.[78] Between 3 and 13 years old, approximately 17% of children experience episodes of confusional arousal.[79] One-third of children who have sleep terrors will go on to experience sleepwalking.[78]

Non-REM parasomnias can occur or worsen when certain "priming factors" are present. Conditions that cause sleep fragmentation, such as OSA, excessive periodic limb movements of sleep, noise, fever, stress, and anxiety, are known precipitants. Conditions that increase N3 sleep, such as sleep deprivation and sedatives (eg, zolpidem), can trigger non-REM parasomnias, as can situational stress.[55] Genetics plays a vital role in the manifestation of parasomnias; patients with a history of sleepwalking are twice as likely to have a first-degree relative who experienced similar events.[78]

A good clinical history with family history alone can establish the diagnosis of a non-REM parasomnia. Overnight PSG is rarely needed for the diagnosis; however, if the clinical history contains features that raise concern for sleep-related seizures (TABLE 11-5[80]) or symptoms suggestive of another sleep disorder such as OSA, an overnight PSG should be obtained. A full 21-lead EEG can be done as part of the PSG to evaluate for seizures such as sleep-related hypermotor seizures (formerly known as nocturnal frontal lobe seizures).[80,81]

Non-REM parasomnia management first involves family education about their typically benign nature and the importance of initiating safety measures at home. Possible safety measures include installing gates at stairs, locking up sharp objects and weapons, and placing alarms on doors and windows. The importance of maintaining a consistent sleep schedule and obtaining the appropriate amount of sleep for the child's age should be discussed since sleep deprivation is a known trigger for non-REM parasomnias. Comorbid sleep disorders such as OSA should be treated. Pharmacotherapy can be considered if the behavior is frequent, leads to daytime sequelae, or is associated with dangerous behaviors. Clonazepam is commonly the first-line treatment for disorders of arousal.

Characteristics of Sleep-related Hypermotor Seizures Versus Non-REM Parasomnias[a] TABLE 11-5

Clinical features	Sleep-related hypermotor seizures	Non-REM parasomnias
Age at onset (years)	11.8 +/- 6.3	Usually <10
Attacks/month	36 +/- 12	1 to 4
Clinical course	Increasing or stable over time	Decreasing over time
Movement semiology	Stereotypic	Polymorphic
Attack onset	Any time during the night	First third of the night
Typical sleep stage	N2 (65% of hypermotor seizures occur during this stage)	N3
Attack duration	Less than 3 minutes (excluding prolonged episodes)	Up to 30 minutes

REM = rapid eye movement.
[a] Data from Derry CP, et al, Sleep.[80]

KEY POINTS

- Conditions that cause sleep fragmentation, such as obstructive sleep apnea and excessive periodic limb movements of sleep, noise, fever, stress, and anxiety, and conditions that increase N3 sleep, such as sleep deprivation and sedatives (eg, zolpidem), can trigger non-REM parasomnia.

- For the diagnosis of definite restless legs syndrome (RLS), children must be able to describe symptoms in their own words. Age-appropriate descriptors are encouraged.

SLEEP-RELATED MOVEMENT DISORDERS

Sleep-related movement disorders are primarily characterized by simple movements that disturb sleep or its onset. These disorders include bruxism, sleep-related rhythmic movement disorder (eg, head banging, head rolling, body rocking), RLS, periodic limb movement disorder, and a newly described sleep disorder called restless sleep disorder.[55] This section focuses on restless sleep disorder and RLS.

Restless Sleep Disorder

In the author's experience, caregivers commonly report restlessness during sleep using descriptive phrases such as "flops like a fish," "wrestling in their sleep," and "tossing and turning." These movements were recently identified as a distinct sleep disorder called pediatric restless sleep disorder, described as frequent recurrent body movements involving large muscle groups during sleep. In addition, the movements persist throughout the night and lead to daytime fatigue, sleepiness, and challenging daytime behaviors.[82] Children with restless sleep disorder have a body movement index score of at least 5 events per hour on PSG. The body movement index is obtained by summing all types of body movement observed on video PSG and dividing it by the total sleep time. Compared to controls, the movements associated with restless sleep disorder lead to arousals, awakenings, and decreased total sleep time. Compared to children with RLS, those with restless sleep disorder do not have increased leg kicking.[82] Consensus diagnostic criteria for restless sleep disorder have been established for children 6 to 18 years old (**TABLE 11-6**).[83] The estimated prevalence of restless sleep disorder in a clinical sleep setting is 7.7%.[84] The pathophysiology of restless sleep disorder is unknown, but there are at least three possible causes: iron deficiency, sleep instability, and sympathetic activation.[85–87] Iron supplementation (oral and IV) improves symptoms (per parent report) in patients with restless sleep disorder.[85]

Restless Legs Syndrome

The *ICSD-3-TR* defines RLS as a sensorimotor disorder characterized by a strong, nearly irresistible urge to move the limbs.[55] The International Restless Legs Syndrome Study Group developed specific guidelines for diagnosing definite pediatric RLS. The symptoms are characterized by the following: (1) unpleasant sensations primarily in the legs, although other body parts like the arms can be affected; (2) an irresistible urge to move the legs due to these sensations; (3) symptoms are alleviated by movement and made worse by rest or inactivity; (4) symptoms are worse in the evening or at night; and (5) the occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition.[88] According to the International Restless Legs Syndrome Study Group guidelines, children must be able to describe symptoms in their own words. Thus, the applicability of the diagnostic criteria depends not on a child's age but rather their verbal and cognitive development. In the report, words and phrases such as "owies," "tickle," "spiders," "boo-boos," "want to run," and "a lot of energy in my legs" are examples of how a child may describe the sensations. Age-appropriate descriptors are encouraged. One can also classify that a child has probable RLS or possible RLS (**TABLE 11-7**[88]). These two classifications are more for research purposes but can still be helpful in clinical practice.[88] The category of "possible RLS" is intended for young children or cognitively impaired children who do not have sufficient language ability to

describe the sensory component of RLS.[87] Pediatric RLS usually progresses more slowly than adult RLS.[55]

RLS is common in school-age children and adolescents, with a prevalence of approximately 2% in the United Kingdom and the United States based on a large study involving an online questionnaire. RLS is more prevalent and severe in adolescents.[55,89] Interestingly, the age of parent-reported symptom onset was less than 8 years old in 78% of patients.[88] This suggests that pediatric RLS is likely underdiagnosed, given the difficulty young children have in describing the symptoms in their own words. Also, patients with neurodevelopmental disorders with limited verbal ability may be misdiagnosed (**CASE 11-2**).

Low iron stores are the leading risk factor for RLS. The incidence of RLS in children with iron deficiency or iron-deficiency anemia is high. Serum ferritin levels less than 50 ng/mL are highly correlated with RLS symptoms.[90] Brain iron insufficiency and altered dopaminergic function appear to play essential roles in RLS development. Impaired iron transport across the blood-brain barrier leads to impaired striatal dopamine neurotransmission.[91] A strong genetic component of pediatric RLS exists, with a high occurrence between monozygotic twins and first-degree sibling pairs.[92,93] An autosomal dominant inheritance with variable penetrance is suggested by familial inheritance patterns.[92]

RLS is diagnosed clinically based on the criteria previously discussed. Several challenges exist with diagnosing pediatric RLS. One is the difficulty children have verbalizing or explaining the symptoms they experience. Finding periodic

Diagnostic Criteria for Restless Sleep Disorder[a] **TABLE 11-6**

All criteria A through H must be met:

A "Restless sleep" as reported by the patient's parent, caregiver, or bed partner, or by the patient

B Movements during sleep involve large muscle groups of the whole body, all four limbs, arms, legs, or head

C Movements occur during sleep or when the individual seems to be asleep

D A total movement index (by video analysis) of 5 or more per hour of sleep is present during video polysomnography

E Restless sleep is reported at least three times per week

F Restless sleep has been present for at least 3 months

G Restless sleep is the cause of clinically significant impairment in behavioral, educational, academic, social, occupational, or other important areas of functioning (eg, daytime sleepiness, irritability, fatigue, mood disturbance, impaired concentration, impulsivity), as reported by the parents, caregivers, or bed partner, or by the patient

H The condition is not better explained by another disorder or factor (eg, sleep-disordered breathing, restless legs syndrome, periodic limb movement disorder, sleep-related rhythmic movement disorder, insomnia disorder, atopic dermatitis, seizure disorder), or the physiologic effects of a substance (eg, caffeine)

Supportive features:

1 Movements during sleep typically occur throughout the whole night

2 No delayed sleep onset is usually reported

[a] Data from DelRosso LM, et al, Sleep.[83]

limb movements on an overnight PSG and a family history of RLS in a first-degree relative is supportive of pediatric RLS.[88] More than five periodic limb movements per hour is abnormal in children and can support the diagnosis. Periodic limb movements are defined as a series of four or more electromyographically identified limb movements that last 0.5 to 5 seconds and occur at intervals of 5 to 90 seconds, typically in non-REM sleep.[48] However, it is important to remember that periodic limb movements and periodic limb movement disorder are distinct from RLS and can occur without RLS.[55] Specific disorders are highly associated with RLS; clinical studies demonstrate a correlation between RLS and ADHD, ADHD symptoms, or both. Up to 44% of children with ADHD have been found to have RLS or RLS symptoms, and up to 26% of children with RLS have been found to have ADHD or ADHD symptoms.[94] RLS may also be underdiagnosed in patients with autism spectrum disorder and may be an unrecognized cause of insomnia in this population. A retrospective study showed that 39% of patients initially presenting with autism and chronic insomnia were diagnosed with RLS.[95] Growing pains are a common RLS mimic; however, growing pains are always described as painful, do not present with the urge to move the legs, and the pain is not relieved by movement.[96]

Iron supplementation is the first-line treatment in pediatric RLS. Checking a patient's blood iron profile and ferritin levels is recommended before beginning oral iron supplementation. If ferritin levels are less than 50 ng/mL, a daily dose of ferrous sulfate (1 mg/kg to 6 mg/kg) or a daily dose of 50 mg to 65 mg of elemental iron is recommended. Taking ferrous sulfate with vitamin C aids with absorption.[97]

CENTRAL DISORDERS OF HYPERSOMNOLENCE

Disorders of hypersomnolence present with excessive daytime sleepiness as the predominant symptom despite sufficient sleep for the person's age. This excessive daytime sleepiness is not otherwise explained by another sleep disorder such as circadian rhythm sleep-wake disorder or sleep-disordered breathing. However, excessive daytime sleepiness often presents differently in children than in adults. Many children with excessive daytime sleepiness present with hyperactivity, inattention, or both. Others extend their nocturnal sleep time and resume daytime napping. Overall vigilance may be decreased. This section concentrates on narcolepsy (primarily type 1) and Kleine-Levin syndrome (KLS).

TABLE 11-7

Diagnostic Criteria for Childhood Restless Legs Syndrome[a]

- **Definite RLS:** The child meets all five essential criteria for restless legs syndrome *and* there is a description, in the child's own words, consistent with leg discomfort
- **Probable RLS:** The child meets all five essential criteria for restless legs syndrome, except criterion 4 (occurrence only or worsening in the evening or night)
- **Possible RLS:** The child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs. The discomfort is characterized by restless legs syndrome criteria 2-5 (is worse during rest and inactivity, relieved by movement, worse in the evening or night, and is not solely accounted for as primary to another medical or behavioral condition)

[a] Data from Picchietti DL, et al, Sleep Med.[88]

Narcolepsy

Narcolepsy is a neurologic disorder of sleep-wake instability characterized by excessive daytime sleepiness, cataplexy, nocturnal sleep disruption, and REM sleep intrusions (eg, sleep paralysis, hypnagogic or hypnopompic hallucinations) that intrude into wakefulness. Narcolepsy is classified as type 1 (without cataplexy) or type 2 (formerly without cataplexy). Cataplexy is muscle atonia associated with strong emotion.[55] The age of highest pediatric incidence is approximately 15 years, with a second peak in the mid thirties.[98] The known incidence of narcolepsy type 1 in adults is 1.2 per 100,000 person-years, with a prevalence of 0.02 to 0.18% in the United States. The incidence and prevalence of

CASE 11-2

A 6-year-old boy with autism spectrum disorder presented with a history of difficulty falling asleep and restless sleep for approximately 6 months. His family reported that they turned off all electronics 1 hour before bed and began his "calming activities," which included a bath and bedtime story. His parents placed him in bed drowsy but awake. He used to fall asleep on his own in about 15 minutes and sleep through the night. He would intermittently cry and say "ow." He was nonverbal and thus unable to tell his parents what was wrong when they went into the room. They noted that he often rubbed his legs against each other at night. Some nights his mother would rub his legs and he would fall asleep faster. Once asleep he stayed asleep, but he was a restless sleeper. He did not have sleep-disordered breathing symptoms. Of note, his mother reported that his diet had become more restricted lately. There was no known family history of restless legs syndrome (RLS).

His examination was notable for poor eye contact and no understandable expressive language. He was able to follow two-step instructions. No other abnormalities were noted on physical examination. RLS was high in the differential diagnosis, but since he was unable to verbalize symptoms in his own words and was a restless sleeper an overnight polysomnogram (PSG) was ordered. The overnight PSG showed no evidence of sleep-disordered breathing, but it did show an increased sleep-onset latency of 48 minutes and an increased periodic limb movement index of 21 events per hour (less than 5 events per hour is normal in children).

Based on the clinical history of observed lower extremity discomfort when lying in bed at night accompanied by motor movement of the affected limbs and the increase in periodic limb movements on the overnight PSG, the patient was diagnosed with possible RLS. Iron studies were obtained. His serum ferritin was 23 ng/mL. He was started on oral iron 3 mg/kg.

COMMENT

This case illustrates that pediatric RLS may present as sleep-onset difficulties. In patients who are nonverbal or too young to describe their symptoms, an overnight PSG will be needed to document elevated periodic limb movements.

narcolepsy type 2 are uncertain.[55] Burgeoning research on the incidence and prevalence of pediatric narcolepsy shows that the number of early-onset narcolepsy cases from 20 pediatric sleep centers across the United States increased by a factor of 2 to 3 after the 2009 H1N1 pandemic.[99] Multiple studies have shown that the diagnosis of narcolepsy is often delayed due to poor recognition and misattribution of symptoms by caregivers and health care providers (CASE 11-3). The Nexus Narcolepsy Registry study found a diagnosis lag of 11.8 years.[100]

The pathophysiologic model for narcolepsy type 1 involves an autoimmune-mediated destruction of orexin-A (hypocretin-1)-containing neurons in the lateral hypothalamus.[101] The hypothesis that narcolepsy is an autoimmune phenomenon is primarily based on the human leukocyte antigen (HLA) association.[102] Associations have been found in most proven autoimmune disorders with specific HLA subtypes. HLA DQB1/06:02 has been identified in over 98% of patients with narcolepsy type 1, which is one of the highest HLA associations. The pathophysiology of narcolepsy type 2 is likely more heterogeneous.[102]

The presentation of narcolepsy in children can be markedly different than in adults. In school-age children, the symptom of excessive daytime sleepiness is not always obvious. The symptoms may present as excessively long nights of sleep or a resumption of previously discontinued daytime napping. Sleep inertia

CASE 11-3

An 8-year-old boy presented to the pediatric sleep clinic with a history of excessive daytime sleepiness and "passing out" spells that started 2 years ago. His grandmother, his main caregiver, noted that he began to sleep 12 to 13 hours nightly around this time. He initially presented to his primary care physician who noted tonsillar hypertrophy on a clinical examination. He was referred to a pediatric otolaryngologist and an adenotonsillectomy was performed. However, his excessive daytime sleepiness continued to worsen, and he began to have sleep spells that happened "out of the blue." He was then referred to pediatric cardiology. The cardiology evaluation consisted of an echocardiogram, which was normal, and 2 weeks of Holter monitoring, which was also normal. His excessive daytime sleepiness and sleep spells continued, and he began to have aggressive behaviors, especially when others tried to wake him from naps. The patient was withdrawn from traditional school after he was tackled by a school resource officer for threatening behaviors after being awakened from sleep in class. He was referred to psychiatry and placed on aripiprazole for mood stabilization. He was referred to pediatric neurology approximately 1. 5 years after his symptoms began. The evaluation by the neurologist included an MRI with and without contrast, which was normal, and admission to the epilepsy monitoring unit. A 3-day epilepsy monitoring unit admission captured his typical aggressive spells, which had no EEG correlate. He was also referred to the pediatric sleep clinic.

In the sleep clinic, his modified Epworth Sleepiness Scale score was 20 out of 24, indicating severe sleepiness. He had to be woken up to perform the physical examination. When awake, his eyes were slightly

(extreme difficulty awakening from sleep), aggressiveness when trying to awaken the child, or both can be seen. Sleep attacks may be longer in children and not as refreshing as they are in adults.[103] In the author's clinical experience, aggressiveness upon awakening can lead to disciplinary actions at school after teachers or schoolmates try to awaken a child. Excessive daytime sleepiness can also present as an increase in irritability, social withdrawal, and shyness.[103] Excessive daytime sleepiness in adolescents may be perceived as laziness; more than one-half of their day is spent in a classroom setting, and excessive daytime sleepiness during a passive activity like sitting can be interpreted as misbehavior by teachers.[104]

The official definition of cataplexy is muscle atonia (complete or partial) associated with strong emotion, particularly mirth.[55] However, in children, cataplexy can occur without an external emotional trigger.[105] Frequently children with narcolepsy will say, "I was thinking of something funny" or "I felt anxious" before the onset of cataplexy. Cataplexy attacks occurring when caregivers chide a child, during sports activities, while approaching caregivers, or while eating are frequently reported.[105] The other important difference is that pediatric cataplexy often presents as facial hypotonia with bilateral ptosis, mouth opening, and tongue protrusion. This presentation has been coined *cataplectic facies*. Perioral dyskinesia or dystonic movements can be present.[105,106] This distinctive presentation of cataplexy may be misdiagnosed as a neuromuscular disorder or

closed, his mouth would hang open, and his tongue would intermittently protrude. His oropharynx appeared normal. His cranial nerves and motor strength were normal, but his general motor tone was low. His reflexes were depressed throughout. His cerebellar examination and gait were normal.

An overnight polysomnogram (PSG) followed by a multiple sleep latency test was ordered to evaluate for narcolepsy. His PSG showed a short sleep-onset latency of 3 minutes and multiple short awakenings during the night lasting less than 1 minute. His sleep efficiency was within normal limits (90%). The PSG did not show sleep-disordered breathing. On a multiple sleep latency test his mean sleep latency was 5.4 minutes and sleep-onset REM periods were noted in three out of five naps. Based on his clinical symptoms of excessive daytime sleepiness despite sufficient sleep for his age, cataplexy, and confirmatory diagnostic testing, he was diagnosed with narcolepsy type 1. He was started on modafinil to treat his excessive daytime sleepiness and venlafaxine to treat his cataplexy.

COMMENT

This case illustrates the diagnostic delay that can occur in children with narcolepsy. This scenario highlights symptoms of excessively long nights of sleep and aggressiveness upon being awoken. Cataplexy can occur without an external trigger in children and can manifest as facial hypotonia in those with pediatric narcolepsy type 1.

KEY POINTS

- Low iron stores are the leading risk factor for RLS. Serum ferritin levels lower than 50 ng/mL are highly correlated with RLS symptoms.
- Clinical studies demonstrate a correlation between RLS and attention deficit hyperactivity disorder.
- Growing pains are a common mimic of RLS. However, growing pains are always described as painful and do not present with the urge to move the legs; the pain is not relieved by movement.
- The pathophysiological model for narcolepsy type 1 involves autoimmune-mediated destruction of orexin-A (hypocretin-1)-containing neurons in the lateral hypothalamus.
- In children, cataplexy can occur without an external emotional trigger.

even a movement disorder. The initial presentation of cataplexy progressively develops into the typical adult presentation of cataplexy as the child gets older.[105] REM sleep intrusions can also present differently in children. The bizarre nature of sleep-related hallucinations and sleep paralysis may confuse children, and they may be embarrassed to discuss the nocturnal phenomena.[104]

Endocrine and metabolic changes occur in narcolepsy type 1 starting at disease onset, potentially related to the involvement of adjacent hypothalamic structures. More than 50% of children with pediatric narcolepsy type 1 fall into the overweight or obese category.[107,108] Body weight may increase quickly and prominently at disease onset. More than 80% of children with narcolepsy type 1 experience rapid weight gain close to symptom onset.[108] Pediatric patients with the rapid weight gain phenotype tend to be sleepier, younger, and have a higher prevalence of obesity and a higher risk of developing long-term obesity.[109] Precocious puberty occurs in 17% of pediatric patients with narcolepsy compared to 1.9% in children with obesity who do not have narcolepsy.[107] Recognition of excessive daytime sleepiness in association with precocious puberty or rapid weight gain as part of pediatric narcolepsy type 1 may help in early detection.[104]

Adults and children with narcolepsy have demonstrated psychosocial dysfunction. Behavioral problems, mood disorders, problems in social functioning, and ADHD are very common in pediatric narcolepsy. Studies show high rates of internalizing problems associated with aggressive behaviors; depression and anxiety are common.[110,111] Compared with people without narcolepsy, children with narcolepsy have an increased risk of experiencing clinically significant depression. The depressive symptoms are often expressed as fatigue.[112] One study found that these symptoms were more profound the younger the child.[109] Pediatric patients with narcolepsy have an overall decrease in quality of life; children younger than 18 years old may have more co-occurring conditions. Children with narcolepsy have respiratory and mood disorders more often than controls.[113] Psychosocial challenges underscore the importance of early diagnosis to reduce disease burden. Regular care should include behavioral and mental health screening for pediatric patients with narcolepsy.

The multiple sleep latency test (MSLT) is the gold standard test for the assessment of hypersomnolence and confirms narcolepsy when the patient has a mean sleep latency of 8 minutes or less and two or more REM periods (sleep-onset REM periods) on the MSLT.[55] In particular, the diagnosis of narcolepsy type 1 can be made when cataplexy is present with the above-described MSLT findings or a sleep-onset REM period (within 15 minutes of sleep onset) on nocturnal polysomnogram. A recent study to validate the MSLT for the diagnosis of pediatric narcolepsy type 1 found that at least two sleep-onset REM periods or a mean sleep latency of 8.2 minutes or less on the MSLT is a valid and reliable marker for pediatric narcolepsy type 1 diagnosis. This differs from the accepted adult MSLT criteria.[114] A diagnostic alternative is to obtain CSF orexin (hypocretin) levels, which are less than 110 pg/mL in people with narcolepsy type 1. A recently developed pediatric hypersomnolence survey has high sensitivity and specificity for narcolepsy and can serve as a good screening tool.[115]

Because narcolepsy is a lifelong chronic disease, long-term medical management is ultimately required to control symptoms. Nonmedical

conservative management such as scheduled napping enhances pharmacologic management. To reap the greatest benefit, consistent bedtime and sufficient sleep duration should be paired with scheduled napping.[116] Wake-promoting medications, such as modafinil, armodafinil, and stimulant medications (eg, methylphenidate and amphetamine derivatives), are used off-label to control excessive daytime sleepiness in children. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants can be used to treat cataplexy.[117] Of all the drugs used to treat the symptoms of narcolepsy, sodium oxybate is the only one approved by the FDA and the European Medicines Evaluation Agency for use in children and adolescents.[118] Sodium oxybate and oxybate salts are given at night and effectively treat disrupted nocturnal sleep, excessive daytime sleepiness, and cataplexy.[118] A lower-sodium version of sodium oxybate was approved in 2020. Pitolisant is a first-in-class medication for the treatment of narcolepsy, with a different mechanism of action. Pitolisant is a selective histamine 3 receptor antagonist and inverse agonist that increases histamine synthesis, release, and transmission in the brain. Pitolisant is FDA-approved for the treatment of excessive daytime sleepiness in adults. In a multicenter, open-label trial evaluating the tolerability and pharmacokinetic profile of pitolisant in 25 children and adolescents, pitolisant was well tolerated, with pitolisant serum concentration being higher in children than adults with the same dose exposure (17.8 mg).[119] A randomized controlled trial in children and adolescents to evaluate the safety and efficacy of pitolisant is ongoing.[119]

In 2021, the American Academy of Sleep Medicine issued new guidelines for treating central disorders of hypersomnolence. These guidelines gave a conditional recommendation for the use of modafinil and sodium oxybate in pediatric patients with narcolepsy.[120] A joint guideline from the European

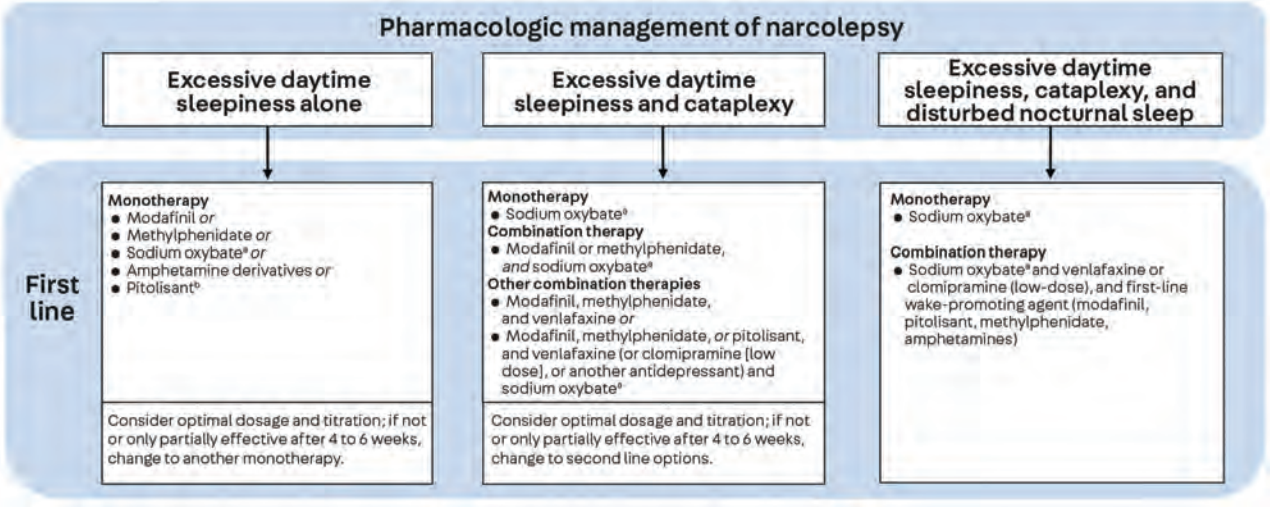

FIGURE 11-3

European guideline and expert statements on the management of narcolepsy in adults and children.

[a] Consider sleep apnea screening before starting sodium oxybate.

[b] Preliminary, needs further results from clinical trials and clinical experience.

Reprinted from Bassetti CLA, et al, J Sleep Res.[121] © 2021 The Authors.

KEY POINTS

- Body weight may increase quickly and prominently at disease onset in children with narcolepsy.
- Precocious puberty occurs in 17% of pediatric patients with narcolepsy compared to 1.9% in children with obesity who do not have narcolepsy.
- Behavioral and mental health screening should be a part of regular care for patients with pediatric narcolepsy.
- Nonmedical conservative management such as scheduled napping enhances pharmacologic management of narcolepsy. To reap the greatest benefit, consistent bedtime and sufficient sleep duration should be paired with scheduled napping.
- The key features of Kleine-Levin syndrome are hypersomnia, cognitive dysfunction, and a feeling of derealization. Hyperphagia and hypersexuality occur together in about 45% of cases.

Academy of Neurology, the European Sleep Research Society, and the European Narcolepsy Network was published with more directed recommendations for the treatment of pediatric narcolepsy based on the primary symptoms (FIGURE 11-3).[121]

Kleine-Levin Syndrome

KLS is a unique disorder of relapsing and remitting episodes of excessive sleepiness and prolonged total sleep time. Symptom onset typically occurs in late adolescence, but cases have been reported in younger and older individuals. KLS has a male predominance and the prevalence is unknown, but it is rare.[122] The diagnostic criteria for KLS include at least two distinct episodes of 2 days to 5 weeks. The episodes usually occur more than once per year but at least once in 18 months. At least during the first years of the syndrome, the individual has normal or near normal sleep and wakefulness, cognition, behavior, and mood between episodes.[55] The discrete episodes contain severe hypersomnia and at least one of the following: cognitive dysfunction, derealization, extreme apathy and disinhibited behavior (hypersexuality or hyperphagia).[55] Hyperphagia and hypersexuality only occur together in about 45% of individuals.[123] During episodes, patients are difficult to awaken but they are arousable. Extreme apathy is present.[123] A common description is that the patient secludes themselves in their room for 15 to 21 hours per day for 1 week to several weeks. Sleep can occur during the night or day with no clear circadian rhythm, and spontaneous waking at any time is possible (mainly to void or eat). The frequency and duration of episodes are not predictable.[123] The median course of the disease is 15 years, and toward the end of the disease course, attacks will become less frequent and less intense before abating completely.[122,123] It has been suggested that a predisposing event occurs before the onset of KLS symptoms; identifiable triggers for the first episode include infections (72%), alcohol intake (23%), sleep deprivation, unusual stress, and head trauma.[122] The symptoms of apathy, derealization, and disinhibition suggest that the association cortices are involved.[122] During KLS episodes, functional brain imaging is abnormal. A recent study evaluating fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) at the time of KLS diagnosis found that 70% of patients had hypometabolism primarily affecting the posterior associative cortex and the hippocampus.[124]

There are no randomized controlled trials evaluating medications to prevent episodes or treat an active bout of KLS. A prospective, open-label, controlled study found that lithium was efficacious in preventing episodes. In the study, serum lithium levels were maintained between 0.8 mmol/L and 1.2 mmol/L (measured 12 hours after administration). Thirty-five percent of people on lithium (compared with 3% of those not on lithium) had complete cessation of KLS episodes. Forty-five percent of individuals had less frequent and less severe KLS episodes.[125]

CONCLUSION

The importance of sleep across the lifespan cannot be underestimated. Sleep and its characteristics change dramatically as people age. Restorative sleep

is vital in all aspects of child development. Untreated sleep disorders can have long-lasting effects on a child's cognitive, physical, and psychosocial well-being.

USEFUL WEBSITES

PEDIATRIC HYPERSOMNOLENCE SURVEY
This screening tool can be used in clinical offices and the community to assess sleepy kids and teens.

wakeupnarcolepsy.org/news/boston-childrens-hospital-pediatric-hypersomnolence-survey/

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Sleep Deprivation and Its Consequences

By Oleg Y. Chernyshev, MD, PhD

ABSTRACT

OBJECTIVE: **This article reviews the clinical, cognitive, behavioral, and physiologic consequences of sleep deprivation in relation to general neurology practice.**

LATEST DEVELOPMENTS: **Despite being one of the most common sleep problems in modern society, the role of sleep deprivation is underrecognized and underestimated in clinical medicine and general neurology practice. The recognition, diagnosis, and management of sleep deprivation in neurologic practice have only recently received close attention. The consequences of sleep deprivation involve all aspects of general neurology practice, including individuals with neurologic disease, neurologists, communities, and health care systems. The identification and timely management of sleep deprivation symptoms may help to improve symptoms of underlying primary neurologic disorders.**

ESSENTIAL POINTS: **This article emphasizes complexities related to the identification and evaluation of sleep deprivation in general neurology practice and describes the consequences of sleep deprivation. By recognizing sleep deprivation in patients with neurologic conditions, the neurologist can provide comprehensive care and contribute to improved clinical and neurologic outcomes.**

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INTRODUCTION

Sleep deprivation, or sleep insufficiency, is the state of cerebral functional disintegration and dysregulation caused by internal or external sleep-disrupting factors directly compromising the quantity or quality of sleep. Current evidence from the American Academy of Sleep Medicine and the Sleep Research Society supports the general recommendation of regularly obtaining 7 or more hours of sleep per night to promote optimal health among adults 18 to 60 years old.[1,2] Regularly obtaining less than 7 hours of total sleep time per 24-hour period is associated with adverse health consequences, including increased mortality, cerebrovascular disease, cardiovascular disease, arterial hypertension, metabolic syndrome, obesity, diabetes, impaired neurocognitive performance with increased accidents and occupational errors, depression, impaired immune function, increased cancer risk, and pain intolerance.[3,4]

CLINICAL DEFINITIONS OF SLEEP DEPRIVATION

According to the *International Classification of Sleep Disorders, Third Edition, Text Revision* (*ICSD-3-TR*), the clinical term for sleep deprivation is insufficient sleep syndrome.[5] Given the heterogenic nature of sleep deprivation, the following alternate names are widely used to describe sleep deprivation in clinical practice: *behaviorally induced insufficient sleep syndrome*, *insufficient nocturnal sleep*, *chronic sleep deprivation*, and *sleep restriction*. The diagnosis of insufficient sleep syndrome can be established when a patient has daily periods of the irrepressible need to sleep, daytime lapses into sleep, or, in the case of prepubescent children, behavioral abnormalities attributable to sleepiness. The patient's sleep time is usually shorter than expected for their age. The curtailed sleep pattern is present most days for at least 3 months. Sleep time is shortened by such measures as an alarm clock or being awakened by another person, and the patient generally sleeps longer when such measures are not used, such as on weekends or vacations. Extending total sleep time results in the resolution of sleepiness and associated daytime impairment symptoms. The clinician should exclude other untreated sleep disorders, the effects of medications or drugs, or other medical, neurologic, or mental health conditions that could be responsible for the patient's excessive daytime sleepiness symptoms. The insufficient sleep syndrome diagnosis is usually based on clinical presentation, history, and supportive data from sleep diaries or actigraphy recordings (TABLE 12-1).[5]

The diagnosis of environmental sleep disorder is controversial but may accompany the diagnosis of insufficient sleep syndrome and provides the identifiable description of sleep disruptive forces, leading to symptoms of insufficient sleep syndrome. The symptoms of environmental sleep disorder are typically characterized by difficulties with sleep initiation, maintenance, or both, that directly result from the influence of an environmental factor. Associated symptoms such as daytime sleepiness, fatigue, or cognitive and emotional

ICSD-3-TR Diagnostic Criteria for Insufficient Sleep Syndrome[a]

TABLE 12-1

***International Classification of Sleep Disorders, Third Edition, Text Revision* criteria A through F must be met for an insufficient sleep syndrome diagnosis:**

- **A** The patient has daily periods of irrepressible need to sleep or daytime lapses into drowsiness or sleep or, in the case of prepubescent children, there is a complaint of behavioral abnormalities attributable to sleepiness.
- **B** The patient's sleep time, established by personal or collateral history, sleep logs, or actigraphy, is usually shorter than expected for their age.
- **C** The curtailed sleep pattern is present on most days for at least 3 months.
- **D** The patient curtails sleep time by such measures as an alarm clock or being awakened by another person and generally sleeps longer when such measures are not used, such as on weekends or vacations.
- **E** Extension of total sleep time results in the resolution of the symptoms of sleepiness.
- **F** The symptoms and signs are not better explained by a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication or substance use or withdrawal.

[a] Reprinted with permission from the American Academy of Sleep Medicine.[5] © 2023 American Academy Of Sleep Medicine.

disturbances may be present. Environmental disturbances may include noise, light, temperature, a bed partner's movement, emotional stimuli, or occupational, familial, or social responsibilities. Environmental disturbances, anxiety, pain, and medical care may exacerbate sleep disruption during hospitalization. If an environmental factor is determined to be the primary cause of a sleep disturbance, a diagnosis of environmental sleep disorder or other sleep disorder may be made.[5]

TYPES OF SLEEP DEPRIVATION

The classification of sleep deprivation reflects compromised sleep quality (ie, continuity, stability, and regularity of sleep), sleep quantity (ie, sleep duration), or both.[3,6] Total sleep deprivation (also called *acute total sleep deprivation*) refers to a single extended period of wakefulness of more than 24 hours. Partial sleep deprivation (also called *chronic sleep deprivation*, *accumulated sleep deprivation*, *chronic sleep insufficiency*, or *sleep restriction*) refers to a chronically restricted, inadequate sleep duration per 24-hour period for two or more consecutive nights. Sleep stage–specific sleep deprivation refers to the selective disruption or suppression of specific stages of sleep and is categorized as either rapid eye movement (REM)-specific sleep deprivation or non-REM-specific sleep deprivation. REM-specific sleep deprivation or suppression can be caused by specific REM-suppressing medications (eg, selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, nicotine, phenelzine, tranylcypromine), by reactive response to stress events (emotional or physical), or as sequelae of posttraumatic stress disorder. Pharmacologic interventions (eg, withdrawal from alcohol, use of theophylline, caffeine) could specifically target stage N3 slow-wave sleep, causing non-REM-specific sleep deprivation.

Sleep fragmentation refers to disrupted sleep continuity and stability per 24-hour period for one or more consecutive nights. Sleep fragmentation may affect the duration of total sleep time per 24-hour period, leading to either its reduction (<7 hours) or extension (>7 hours).[3,6]

EPIDEMIOLOGY

The prevalence of sleep deprivation causing excessive daytime sleepiness is between 9% and 24%.[7] Sleep deprivation from either insufficient sleep time or sleep disorders is a significant public health problem affecting approximately 50 to 70 million Americans.[8,9] In a population-based survey, approximately 30% of adults reported a sleep duration of less than 7 hours per night on weekday or workday nights.[10-12] Sleep deprivation is highly prevalent in populations with lower socioeconomic status. Sleep deprivation is more prevalent among Black Americans compared to White Americans and is frequent among Hispanic Americans, non-Hispanic Black Americans, American Indian and Alaskan Natives, Native Hawaiians and Pacific Islanders, and younger adults (<65 years old).[11-17] The prevalence of sleep deprivation is elevated in professional environments with extended work hours, rotating or shift work, and increased job-related stress.[18,19]

MORBIDITY AND MORTALITY

A self-reported short sleep duration (often defined as ≤6 hours, with a range of 5 to 7 hours) is commonly associated with impaired vigilance, weight gain, obesity, diabetes, and cardiovascular disease, as well as an elevated risk (12%)

for all-cause mortality. People reporting consistently sleeping 5 hours per night or less should be regarded as a higher risk group for all-cause mortality.[20,21]

Interestingly, a paradoxical U-shaped relationship exists between daily sleep duration and all-cause mortality with a nadir at 7 hours per 24-hour period. Pooled analyses indicate that short sleepers (<7 hours per night, often <5 hours per night) have a 12% greater risk of mortality and long sleepers (commonly >8 or 9 hours per night) have a 30% greater risk of mortality than those sleeping 7 to 8 hours per night. The increased all-cause mortality in people sleeping 9 hours or more per night may reflect the compensatory increase of total sleep time in response to sleep fragmentation caused by underlying pathology and may represent a useful diagnostic clinical tool for suspected subclinical or undiagnosed comorbidity.[20]

CLINICAL CONSEQUENCES OF SLEEP DEPRIVATION

Both short-term and long-term sleep deprivation lead to the development of physiologic and neurobehavioral problems (FIGURES 12-1 and 12-2),[3,4,22] reduced quality of life, and increased mortality.[23]

Neurologic Consequences of Sleep Deprivation

The neurologic effects of sleep deprivation include impaired memory, judgment, and decision making. Sleep deprivation can also lead to difficulty with focus and concentration, irritability,[24] circadian disruption, hallucinations, impulsivity, delirium, psychosis, and suicidal behavior.[25-27] Sleep deprivation increases the risk for seizures, strokes, headaches, and Alzheimer disease.[28,29]

Chronic restriction of sleep to 6 hours or less per night over 14 consecutive days produces significant cumulative, dose-dependent deficits in cognitive performance on all tasks, equivalent to cognitive performance impairments observed in up to 2 nights of total sleep deprivation.[22]

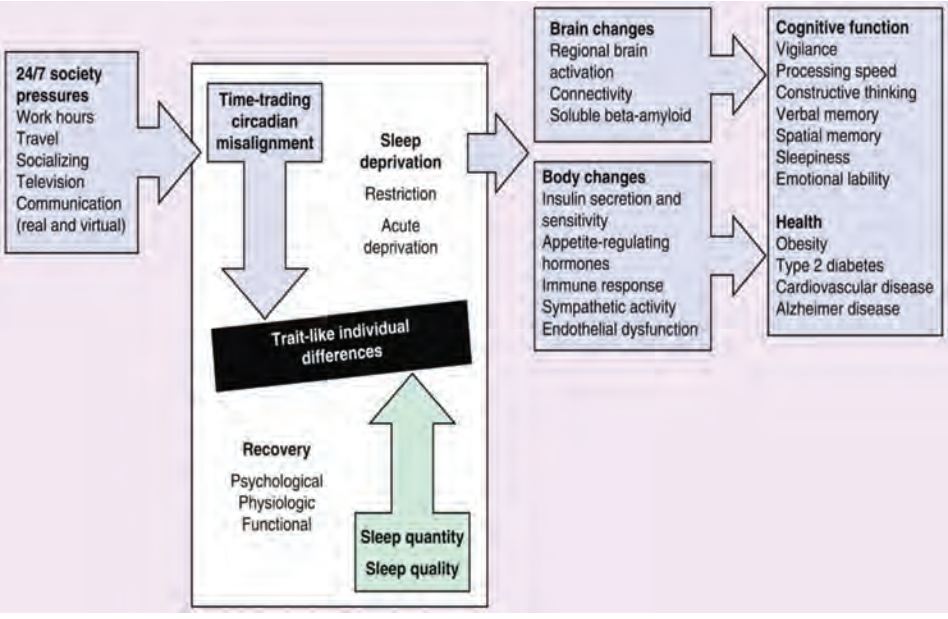

FIGURE 12-1

Conceptual diagram of the effect of societal pressures on overall health through disruption of sleep.

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KEY POINTS

- Sufficient sleep is determined by the adequate duration, continuity, regularity, stability, and quality of sleep.
- Sleep fragmentation refers to disrupted sleep continuity and stability per 24-hour period for one or more consecutive nights.
- Sleep deprivation from either insufficient sleep time or sleep disorders is a significant public health problem affecting 50 to 70 million Americans.
- The prevalence of sleep deprivation is elevated in professional environments with long or extended work hours, rotating or shift work, and increased job-related stress.
- Sleep deprivation impairs functions mediated by the prefrontal cortex that affect working memory and attention.
- The shorter the sleep duration, the greater the cognitive deficits.
- During persistent sleep deprivation, both daytime sleepiness and cognitive impairments continue to progress unless planned sleep occurs.

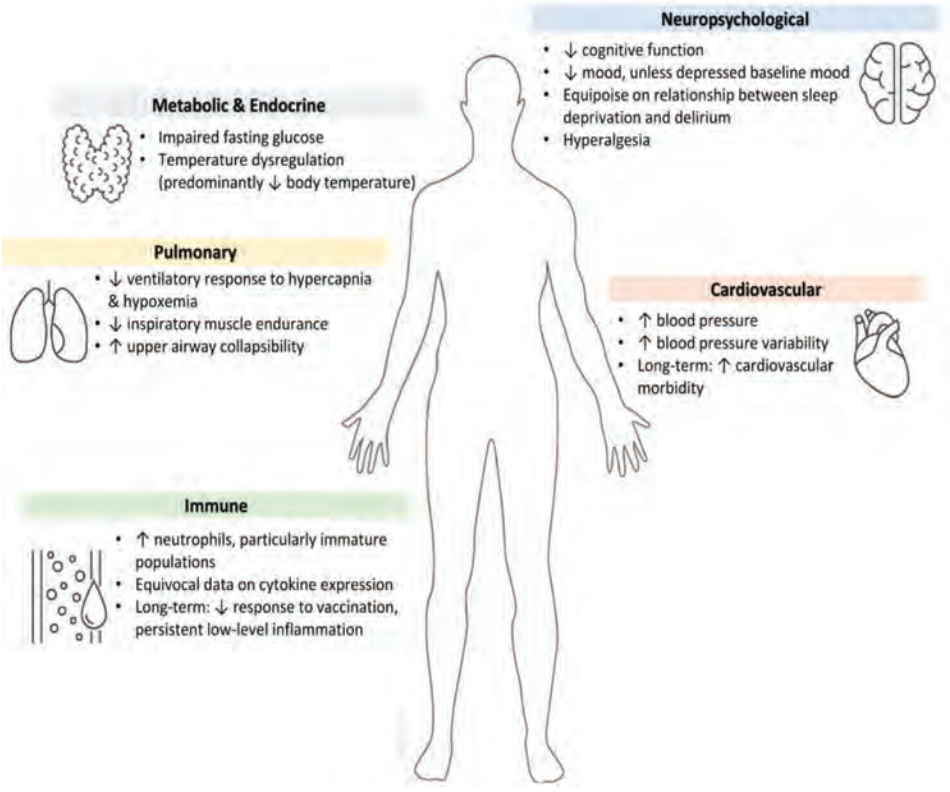

FIGURE 12-2

Impact of sleep deprivation on organ systems in hospitalized patients.

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Sleep deprivation impairs functions mediated by the prefrontal cortex that affect working memory and attention. Vigilant attention is particularly adversely affected by sleep deprivation.[30] Microsleeps reflect shifts in neuronal activity in frontal, thalamic, and secondary sensory processing areas of the brain, leading to wake-state instability.[31] With sleep deprivation accumulation, the duration of microsleeps increases from brief lapses of 0.5 seconds to 10 seconds or more.[32] The wake-state instability is expressed clinically as increased failures to respond to stimuli (errors of omission) as well as increased responses in the absence of stimuli (errors of commission or false responses).[3,30,33,34]

Level 1 evidence demonstrates that cognitive performance involving executive function, vigilance, attention, cognitive processing speed, and working memory, as well as physiologic sleep propensity and drowsy driving, are all sensitive to sleep durations below 7 hours per 24-hour period. Interestingly, rule-based reasoning, decision making, and planning appear to be relatively unaffected by sleep deprivation.[30] Cognitive vulnerabilities increase with declining duration of sleep[2]; the shorter the sleep duration, the greater the cognitive deficits. During persistent sleep deprivation, both daytime sleepiness and cognitive impairments continue to progress unless planned sleep occurs. Self-reported excessive daytime sleepiness ratings usually overestimate the level of alertness after sleep deprivation and do not necessarily reflect objective changes in cognitive performance capability during sleep deprivation.

Chronically sleep-deprived individuals are often unaware of their increasing cognitive deficits and underestimate the negative impact of sleep deprivation on cognition and performance.[35]

In individuals repeatedly exposed to the same acute or chronic sleep deprivation, the neurobehavioral responses to sleep deprivation were found to be consistent and stable, with traitlike patterns of differences in vulnerability.[36] These traitlike differences in vulnerability may reflect underlying genetic differences.[37]

Sleep deprivation and alcohol intoxication demonstrate quantitatively and qualitatively similar effects on cognitive performance. The impairment of cognitive psychomotor performance after 17 hours of sustained wakefulness is equivalent to the effect produced by a blood alcohol concentration of 0.05%, and after 24 hours of extended wakefulness it is equivalent to a blood alcohol concentration of 0.1% (exceeding the legal limit for driving in most states).[38]

Self-reported chronic sleep deprivation is associated with increased cross-sectional and longitudinal risks for depression, whether measured as symptoms or as a diagnosis. The threshold for short sleep varies across studies from 5 to 7 hours, with the majority using 6 hours or less.[2] Sleep deprivation is linked to stress and anxiety disorders,[39-41] and acute sleep deprivation may cause short-term remission of major depressive disorder (in about 50% of patients).[42] However, sleep deprivation may serve as a trigger for manic episodes in patients with bipolar disorder.[3,43] Sleep deprivation results in labile mood, impaired emotional processing, reduced ability to read positive emotional expressions, and increased subjective sleepiness.[44]

In adolescents, sleep deprivation is linked to: (1) poor academic performance; (2) increased irritability, anxiety, loneliness, hyperactivity, impulsiveness, and depression; (3) addiction behavior including the use of illicit drugs, nicotine, and marijuana, cigarette smoking, and drinking alcohol; and (4) aggressive behaviors, driving while intoxicated, suicidal ideation, and having unprotected sex.[39-41,45,46]

Increasing the duration of recovery sleep for one night following chronic sleep deprivation leads to progressive improvements in neurobehavioral performance, but some deficits persist even after 10 hours of recovery sleep.[3]

Sleep Deprivation and the Glymphatic System

Sleep plays a vital neuroprotective role in clearing metabolites produced in the brain via the glymphatic system. The glymphatic system works differently during sleeping and waking states. During sleep, CSF flows more profusely, significantly increasing the elimination of toxic substances from neurons and intercellular spaces. CSF influx into periarterial spaces decreases by about 90% during the waking state, and the interstitial space volume fraction is also 60% lower during this time. When sleep is restricted, the glymphatic system does not have enough time to fulfill this function, leading to the accumulation of toxins and misfolded proteins.[47] The potential impairment of the macroscopic glymphatic system–based clearance of interstitial metabolites contributes to (1) the development of sleepiness due to progressive, wake-induced accumulation of adenosine in the basal forebrain, which drives the homeostatic sleep drive, also referred to as Process S, and (2) the development of neurodegenerative diseases (eg, Alzheimer disease) due to the accumulation of protein aggregates (β-amyloid and tau proteins).[47-49] The glymphatic system may be useful in detoxifying the brain of protein aggregates such as β-amyloid and tau proteins

KEY POINTS

- Chronically sleep-deprived individuals are often unaware of their increasing cognitive deficits and underestimate the negative impact of sleep deprivation on cognition and performance.
- The impairment of cognitive psychomotor performance after 17 hours of sustained wakefulness is equivalent to the effect produced by a blood alcohol concentration of 0.05%, and after 24 hours of extended wakefulness it is equivalent to a blood alcohol concentration of 0.1% (exceeding the legal limit for driving in most states).
- Sleep deprivation is linked to stress and anxiety disorders, and acute sleep deprivation may cause short-term remission of major depressive disorder.
- Increasing the duration of recovery sleep for one night following chronic sleep deprivation leads to progressive improvements in neurobehavioral performance, but some deficits persist even after 10 hours of recovery sleep.
- Sleep plays a vital neuroprotective role in clearing the toxic metabolites produced in the brain via the glymphatic system. During sleep, CSF flows more profusely, significantly increasing the elimination of toxic substances from neurons and intercellular spaces.
- When sleep is restricted, the glymphatic system does not have enough time to fulfill its function of removing toxins and misfolded proteins.

and alpha-synuclein, and in the prevention of secondary neuronal damage due to the accumulation of such molecules after traumatic brain injury. The clearance of brain interstitial solutes and waste is one of the most important biological processes underlying the restorative function of sleep.[50] Sleep deprivation contributes to glymphatic system malfunction and can disrupt these processes. Sleep deprivation increases adenosine levels in the basal forebrain and thereby inhibits the cholinergic system and disrupts the switch between sleep and wakefulness. Experimental sleep deprivation disrupts the physiologic sleep stage–dependent fluctuation of monoamines and changes the density of adenosine and norepinephrine receptors, both of which contribute to the cognitive impairments observed in sleep deprivation.[48-50]

Sleep Deprivation and Pain

Sleep deprivation (<5 to 6 hours per night) is associated with decreased pain tolerance, increased pain sensitivity, and hyperalgesia.[51-55] The selective disruption of non-REM slow-wave sleep causes a lowering of the pain threshold and promotes pain sensitivity.[56] Extended sleep duration (7 to 9 hours per night) is associated with reduced pain symptoms.[52,53,57-59]

Sleep Deprivation and Cerebrovascular Disease

Sleep deprivation exacerbates stroke pathophysiology by increasing the expression of growth-inhibiting genes, neuroinflammation, and oxidative stress.[60] Sleep deprivation following cerebral ischemia increases the expression of the growth-inhibiting gene neurocan (*NCAN*), which encodes a chondroitin sulfate proteoglycan released by astrocytes. Astrocytes and the *NCAN* proteoglycan form a barrier around the ischemic infarct area and inhibit neuronal reconnection. Normal sleep increases the levels of γ-hydroxybutyrate, which has an inhibitory effect on ischemia-induced *NCAN* expression.[61] Since cerebral ischemia activates inflammatory pathways, sleep deprivation during this period aggravates the inflammatory response.[62] Acute total sleep deprivation (40 hours) significantly increases plasma levels of the inflammatory markers interleukin-1β, interleukin-1 receptor antagonist, E-selectin, and ICAM-1.

Sleep Deprivation and Epilepsy

Sleep deprivation and sleep disorders may affect epilepsy by reducing the seizure threshold and facilitating seizure occurrence. Seizures that occur during sleep, the effects of antiseizure medication, and interictal epileptiform activity may serve as sleep-disrupting forces that cause sleep fragmentation. This may lead to a positive feedback loop of disrupted sleep and worsened seizures, the combination of which interferes with sleep's restorative and neuroplastic functions. Seizure rates for each stage of non-REM sleep, specifically the N2 non-REM stage, are significantly higher compared with that for REM sleep. The vulnerability to seizure activity during non-REM sleep may be explained via the synchronized EEG pattern of the non-REM stages of sleep.[63]

Sleep Deprivation and Headache

Sleep deprivation is a common trigger for both episodic and chronic migraine with and without aura and for tension-type headache.[64,65] Patients with migraine and chronic sleep deprivation (<6 hours sleep per night) are more prone to morning headache episodes and have more frequent and more intense headaches

than those who have longer sleep duration.[66,67] The sleep-associated occurrence of attacks in cluster headache can lead to sleep deprivation and contribute to reduced quality of life in these patients.[68]

Sleep Deprivation and Alzheimer Disease

Sleep deprivation impairs the glymphatic and aquaporin-4 channel systems, which results in the aggregation of β-amyloid and tau proteins and accelerates the formation of amyloid plaques and neurofibrillary tangles.[47,50,69] Glymphatic function declines over the middle to terminal stages of Alzheimer disease due to the impaired polarity of aquaporin-4 at the astrocyte end feet.[47,70] The increased accumulation of β-amyloid and tau proteins disrupts the sleep-wake cycle. Sleep deprivation can increase active oxygen species and, as a result, damage mitochondria and induce apoptosis. By activating kinases, sleep deprivation may increase tau phosphorylation and may contribute to the emergence of Alzheimer disease via neuronal degeneration, β-amyloid deposition, and neurofibrillary tangle formation.[3,49]

Sleep Deprivation and Parkinson Disease

Chronic sleep deprivation may contribute to Parkinson disease development via the impairment of nicotinamide adenine dinucleotide–dependent deacetylase sirtuin type 3 activity, which eventually leads to superoxide production in locus coeruleus neurons, mitochondrial protein acylation, neurodegeneration, and neuronal death.[71]

Sleep Deprivation and Multiple Sclerosis

Sleep deprivation contributes to fatigue in multiple sclerosis.[72] Sleep deprivation affects the expression of genes involved in the synthesis and maintenance of myelin proteins, and downregulates the expression of genes involved in oligodendrocyte precursor cell differentiation; these cells are necessary for the formation of new myelin components in both the uninjured and injured brain. Sleep deprivation upregulates the expression of apoptotic and cellular stress response genes, which impedes nerve regeneration in multiple sclerosis.

Individuals working rotating night shifts for at least 3 years before the age of 20 are more susceptible to multiple sclerosis compared with day-shift workers. A possible mechanism behind this increased risk is circadian rhythm disruption and the release of cellular and molecular inflammatory mediators causing neuroimmune dysregulation.[73,74]

Sleep Deprivation and Huntington Disease

In Huntington disease, sleep deprivation worsens cognition, motor function, and depression. Polysomnography in people with Huntington disease shows increased sleep-onset latency, sleep fragmentation, and frequency of awakenings.[75]

PHYSIOLOGIC CONSEQUENCES OF SLEEP DEPRIVATION

Exposure to sleep deprivation causes significant physiologic changes in multiple domains and systems, including genetic, cardiovascular, respiratory, gastrointestinal, metabolic, endocrine, immune, dermatologic, musculoskeletal, renal, urologic, reproductive, and oncologic systems.

KEY POINTS

- The clearance of brain interstitial solutes and wastes is one of the most important biological processes underlying the restorative function of sleep.
- Sleep deprivation (<5 to 6 hours per night) is associated with decreased pain tolerance, increased pain sensitivity, and hyperalgesia.
- The selective disruption of non–rapid eye movement (non-REM) slow-wave sleep causes a lowering of the pain threshold and promotes pain sensitivity. Extended sleep duration (7 to 9 hours per night) is associated with reduced pain symptoms.
- Sleep deprivation exacerbates stroke pathophysiology by increasing the expression of growth-inhibiting genes, neuroinflammation, and oxidative stress.
- Sleep deprivation and sleep disorders may affect epilepsy by reducing seizure threshold and facilitating seizure occurrence.
- The epileptiform discharges and facilitated propagation of seizure activity from the epileptic focus readily occur during the synchronized pattern of non-REM sleep, specifically during the N2 stage.
- Migraine and sleep have a reciprocal relationship. Sleep deprivation is a common trigger for both episodic and chronic migraine with and without aura and for tension-type headache.

Genomic and Proteomic

Sleep deprivation changes homeostatic sleep drive at the molecular levels of gene transcription, translation, and protein synthesis, resulting in elevated cortical expression of the period circadian regulator 1 and 2 (*PER1* and *PER2)* clock genes, which are also associated with disorders observed in circadian rhythm disruption.[76] Sleep deprivation affects the signaling mechanisms that regulate transcription and translation processes involved in memory.[77] Sleep deprivation also increases microglial phagocytic neurodegenerative activity via the expression of the astrocytic genes MER proto-oncogene, tyrosine kinase (*MERTK*) and CRK proto-oncogene, adaptor protein (*CRK*), which are associated with microglial phagocytosis.[78]

Four potential biomarkers of chronic sleep deprivation are kininogen 1 (*KNG1*), profilin-1 (*PFN1*), pyruvate kinase M1/2 (*PKM*), and clusterin (*CLU*). *KNG1* is an inflammatory mediator found in the plasma kallikrein-kinin system that inhibits the aggregation of platelets, enhances brain inflammation, induces leakage in the blood-brain barrier, and generates microvascular thrombosis. *PFN1* is an actin-binding protein that promotes arterial atherosclerosis and cardiac hypertrophy. *PKM* modulates the final stage in glycolysis, enhances cell proliferation, and plays a role in cardiac metabolism. *CLU* is expressed during cell stress and tissue injury and helps to salvage reversibly damaged cardiomyocytes in cardiac disease.[79,80] Chronic sleep deprivation and chronic night-shift work trigger oxidative stress, and may generate an increase in DNA damage and compromise DNA repair processes.[81,82]

Cardiovascular

The effects of sleep disruption on sympathetic activity, glucose metabolism, and inflammation may lead to adverse cardiovascular effects.[83] Chronic sleep deprivation results in impaired autonomic function, which leads to cardiovascular dysfunction.[84] Acute sleep deprivation is associated with increases in heart rate and blood pressure and a reduction in heart rate recovery.[85-87] Chronic sleep deprivation increases blood pressure, heart rate, catecholamine activity, and sympathetic surge, which impairs the physiologic "nocturnal dip" in blood pressure during non-REM sleep.[83,86,88] Chronic sleep deprivation is associated with dysfunctional nitric oxide–mediated endothelium-dependent vasodilation, which significantly contributes to the development of cardiovascular disease, arterial hypertension, and diabetes.[89-91] Prolonged sleep deprivation activates immune responses affecting cholesterol mechanisms, contributing to the development of atherosclerosis.[92] The relative risk of incident hypertension is 1.20 (95% confidence interval, 1.06 to 1.36) in adults with sleep continuity disturbance.[93] In adolescents, higher sleep disturbance scores on the Pittsburgh Sleep Quality Index were associated with higher systolic blood pressure, increased risk of hypertension, higher body mass index, and hypercholesterolemia.[94] Short sleep duration and difficulty maintaining sleep are associated with incident myocardial infarction in middle-aged females.[95]

Respiratory

Sleep deprivation decreases intrinsic ventilatory drive to hypoxic and hypercapnic states by causing decreased chemoreceptor sensitivity to oxygen and carbon dioxide. Sleep deprivation reduces respiratory motor output,

weakens inspiratory muscle strength, and impairs respiratory motor plasticity (ie, inspiratory drive-in response to hypoxia).[96-100] Sleep deprivation alters the modulation of T-helper 1 cell–mediated and T-helper 2 cell–mediated airway hyperresponsiveness with increased immunoglobulin E levels, and induces neutrophilic response and severe airway inflammation, which may precipitate neutrophilic-driven asthma.[101]

Gastrointestinal

Sleep deprivation results in an acute inflammatory response in gastric mucosa, along with an increase in the number of eosinophils in the duodenal villi and periglandular area with an alteration to the dynamic integrity of the mucosal barrier.[102] Sleep deprivation is associated with the risk of nonalcoholic fatty liver disease.[103]

Metabolic and Endocrine

Sleep deprivation is associated with temperature dysregulation, which leads to temperature elevation during the initial stages of sleep deprivation followed by a decline in body temperature. Increased brain temperature and glucose consumption are associated with sleep deprivation, which is confirmed by elevated 2-deoxyglucose uptake and a decline in brain glycogen levels.[104-106] Sleep deprivation is linked to impaired fasting glucose, sustained hyperglycemia, low glucose tolerance, elevated insulin resistance, and diabetes, as well as persistently elevated levels of catabolic immunosuppressive hormones and suppressed levels of anabolic, immunofacilitatory hormones.[83,107-110] Chronic sleep deprivation with sleep reduction greater than 1 hour per night or sleeping 4 hours or less in a single night can decrease glucose sensitivity by 20% to 40% in healthy adults via the modulation of both hepatic and peripheral metabolic pathways.[111] Sleep deprivation is associated with an increase in excessive food intake and weight gain.[112] Sleep deprivation leads to elevated ghrelin (hunger-promoting hormone) and decreased leptin (satiety hormone) levels with an increase in leptin resistance.[113,114] Type 2 diabetes, obesity, and metabolic syndrome occur at higher rates in the setting of chronic sleep deprivation.[115-118] Chronic sleep deprivation (<6 hours per night) is also associated with higher nonfatal cardiovascular events and obesity.[119] Increases in central obesity and metabolic syndrome, higher levels of fasting glucose, blood pressure, and triglycerides, and a reduction in the level of high-density lipoprotein cholesterol are all seen in the setting of sleep deprivation.[120]

Immune Response

Sleep deprivation is associated with a decreased vaccine immune response and a higher risk of developing pneumonia or an upper respiratory infection following rhinovirus exposure.[121-125] Sleep deprivation decreases natural killer cell function and activity by approximately 30% and reduces mobilization and extravasation of adapter T-cells.[126,127]

Genitourinary

Increased diuresis, renal sodium excretion, nocturnal urine production, proteinuria, and possibly prostate cancer are associated with sleep deprivation.[128] Experimental sleep deprivation in men results in sexual dysfunction, decreased

KEY POINTS

- The sleep-associated occurrence of attacks in cluster headache can lead to sleep deprivation and contribute to reduced quality of life.
- Sleep deprivation impairs the glymphatic and aquaporin-4 channel systems, which results in the aggregation of β-amyloid and tau proteins and accelerates the formation of amyloid plaques and neurofibrillary tangles.
- Sleep deprivation changes homeostatic sleep drive at the molecular levels of gene transcription, translation, and protein synthesis, resulting in elevated cortical expression of the period circadian regulator 1 and 2 (*PER1* and *PER2)* clock genes, which are also associated with disorders observed in circadian rhythm disruption.
- Sleep deprivation affects the signaling mechanisms that regulate transcription and translation processes involved in memory.
- The effects of sleep disruption on sympathetic activity, glucose metabolism, and inflammation may lead to adverse cardiovascular effects.
- Acute sleep deprivation is associated with increases in heart rate and blood pressure and a reduction in heart rate recovery.
- Sleep deprivation increases blood pressure, heart rate, catecholamine activity, and sympathetic surge, which impairs the physiologic "nocturnal dip" in blood pressure during non-REM sleep.

KEY POINTS

- Sleep deprivation decreases intrinsic ventilatory drive to hypoxic and hypercapnic states by causing decreased chemoreceptor sensitivity to oxygen and carbon dioxide. Sleep deprivation reduces respiratory motor output, weakens inspiratory muscle strength, and impairs respiratory motor plasticity (ie, inspiratory drive-in response to hypoxia).
- Sleep deprivation is associated with temperature dysregulation, which leads to temperature elevation during the initial stages of sleep deprivation followed by a decline in body temperature.
- Sleep deprivation is linked to impaired fasting glucose, sustained hyperglycemia, low glucose tolerance, elevated insulin resistance, and diabetes mellitus, as well as persistently elevated levels of catabolic immunosuppressive hormones and suppressed levels of anabolic, immunofacilitatory hormones.
- Sleep deprivation is associated with an increase in excessive intake of food and weight gain.
- Increases in central obesity and metabolic syndrome, higher levels of fasting glucose, blood pressure, and triglycerides, and a reduction in the level of high-density lipoprotein cholesterol are all seen in the setting of sleep deprivation.

sexual behavior, lower testosterone levels, and alterations of sperm function and viability.[129]

Cancer

Short sleep duration (<6 hours) is associated with breast cancer, colorectal adenoma, and colorectal cancer.[130-132]

Safety Consequences of Sleep Deprivation

Sleep deprivation is responsible for adverse events related to occupational-related errors and motor vehicle accidents. An estimated 10% to 15% of fatal motor vehicle accidents are related to sleep deprivation. Motor vehicle accident risk also increases when self-reported sleep duration is less than 6 to 7 hours.[2,133]

Sleep Deprivation in Hospitalized Patients

The hospital environment can disrupt sleep for many patients, eventually causing acute or chronic sleep deprivation with resultant multiorgan clinical consequences (**FIGURE 12-2**).[4] Patient care activities, especially noise level, consistently rank as a major source of sleep disturbance in surveys of patients in the intensive care unit (ICU). Hospitalization itself is associated with higher morning blood pressure in older adults.[134] In the ICU setting, patients reported from 1 to 42 sleep-disruptive interactions per 7 PM to 7 AM shift.[135,136]

The noise level in a typical ICU is markedly higher than the levels recommended by the World Health Organization and Environmental Protection Agency (50 dB to 90 dB in the ICU versus the recommended 20 dB to 45 dB) (**CASE 12-1**).[4]

Medications and Pharmacologic Effects

Medications commonly used in both outpatient and inpatient settings can disturb sleep via pharmacologic effects on sleep neurophysiology and sleep architecture.[4] While opioids have a sedative effect, they decrease total sleep time and duration of time spent in the N3 and REM sleep stages. Benzodiazepines, while widely used for insomnia management, suppress REM and N3 sleep in favor of N2 sleep in healthy individuals. Vasopressors and beta-blockers disrupt sleep via their impacts on melatonin production. Antidepressants suppress REM sleep. Diuretics and IV drips may augment diuresis, urinary frequency, and nocturia, and may necessitate the use of uncomfortable indwelling urinary catheters. Corticosteroids decrease REM sleep and may cause nightmares.

Patient-Specific Factors

Illness severity has been positively correlated with sleep disturbance. Pain, either in association with illness severity or on its own, usually causes decreased quality and quantity of sleep due to frequent arousals. Mechanical ventilation can disturb sleep due to ongoing mismatch between patient demand and ventilator supply. Data from numerous studies indicate that patient-ventilator mismatch, rather than any given ventilator mode, is most responsible for sleep disturbance.[139] Although the relevance of specific sleep deprivation–related effects to hospital and long-term outcomes requires further description, it is evident that low-quality sleep impairs patients' subjective well-being.[134,139]

CASE 12-1

A 27-year-old woman with a history of stable migraine with aura was brought to the trauma center following a motor vehicle accident. She was noted to have a scalp frontal hematoma and concussion with brief loss of consciousness. She reported a feeling of "brain fog" since that morning, along with sleepiness. She reported that since her baby was born 4 months ago, she was "very short" on sleep, averaging about 5 to 7 hours per night. She slept only 3 hours the previous night because she was tending to her crying baby and spending time online. Her neurologic examination was unremarkable. Her Epworth Sleepiness Scale score was 24/24 (the highest subjective measure of sleepiness). Initial noncontrast head CT and CT angiography of the head and neck were normal. The patient was admitted to the intensive care unit with hourly neurologic assessments per protocol. Around 5 AM she became very agitated and reported a right-sided throbbing headache with nausea that she described as a typical migraine. Her neurologic examination was reassuring, and emergent neuroimaging and CSF analysis did not show acute pathology. She was given calcitonin gene-related peptide antagonist and antiemetics and was allowed to sleep with the use of earplugs in a quiet private intensive care unit room during the day with overnight neurochecks every 3 hours. After sleeping 14 hours, the patient was awake, alert, and oriented without any headache, nausea, or any signs of focal neurologic deficits.

COMMENT

This patient demonstrated many signs and symptoms meeting the criteria for both acute and chronic sleep deprivation (insufficient sleep syndrome [TABEL 12-1]),[5] including excessive daytime sleepiness and difficulty concentrating. Her symptoms started after the birth of her baby 4 months prior (meeting the ≥3 months criterion for insufficient sleep syndrome in the *International Classification of Sleep Disorders, Third Edition, Text Revision* [*ICSD-3-TR*] [TABLE 12-1])[5] and were associated with chronic sleep restriction related to child care (meeting the *ICSD-3-TR* criterion for excessive daytime sleepiness).[5]

In this case, preadmission sleep deprivation coupled with hourly neurologic assessments worsened her sleep deprivation and may have triggered her migraine attack.[64,137,138] The resolution of sleep deprivation symptoms after obtaining 14 hours of protected, uninterrupted sleep (through the use of earplugs and reduced frequency of neurologic assessments) confirmed the diagnosis of insufficient sleep syndrome in the setting of hospital admission. Sleep deprivation is a frequent trigger for the development of delirium or acute encephalopathy in hospitalized patients.[25-27]

KEY POINTS

- Sleep deprivation is associated with a decreased vaccine immune response and a higher risk of developing pneumonia or an upper respiratory infection following rhinovirus exposure.
- Data from numerous studies indicate that patient-ventilator mismatch, rather than any given ventilator mode, is most responsible for sleep disturbance.
- Sleep deprivation is very common among medical students, residents, and practicing physicians, leading to health problems, medical errors, professional burnout, marital problems, motor vehicle accidents, depression, suicidality, and addiction.
- Sleep deprivation in night-shift workers and medical practitioners leads to significant increases in blood pressure, heart rate, heart contractility, and stress hormone secretion.
- Fragmented and insufficient sleep has been hypothesized as a potential mechanism that promotes burnout.

EVALUATION AND MANAGEMENT OF SLEEP DEPRIVATION IN NEUROLOGIC PRACTICE

The role of sleep deprivation is often underrecognized and underestimated in clinical medicine and general neurology practice. The timely recognition, diagnosis, and management of sleep deprivation in patients and health care providers are critical in neurologic practice. In English-speaking literature reviews, there are no defined and validated systematic tools, protocols, or algorithms for sleep deprivation recognition or screening in clinical practice. The clinical evaluation should include discussions of total sleep time, sleep-wake timings, and subsequent symptoms experienced during wakefulness. In people with neurologic disease, potential etiologies of sleep deprivation include circadian misalignment, pharmacologic effects, medical comorbidities, social and environmental factors, and comorbid sleep disorders.

Sleep Deprivation and Burnout in Health Care Providers

Sleep deprivation is very common among medical students, residents, and practicing physicians, leading to health problems, medical errors, professional burnout, marital problems, motor vehicle accidents, depression, suicidality, and addiction.[140,141] Sleep deprivation in night-shift workers and medical practitioners leads to significant increases in blood pressure, heart rate, heart contractility, and stress hormone secretion.[142]

Fragmented and insufficient sleep has been hypothesized as a potential mechanism that promotes burnout. Sleep effects of burnout include a hyperarousal state that can facilitate sleep-initiation insomnia, sleep-maintenance insomnia, or both. This scenario leads to reduced sleep quality and cyclical sleep disturbance, which plays an important role in the persistence of burnout symptomatology.

Data suggest that the reversibility of burnout may be contingent on more optimized sleep. Among individuals who experienced burnout and stopped working to pursue self-care, those who were able to achieve recommended amounts of sleep recovered more quickly.[141]

CONCLUSION

Sleep deprivation results in impaired memory, judgment, and decision making. It also leads to difficulty in focusing and concentration, irritability,[24] circadian disruption, and increased risk for hallucinations, impulsivity, delirium, psychosis, and suicidal behavior.[25–27] Sleep deprivation increases the risk for seizures, strokes, headaches, and Alzheimer disease. Specific causes of sleep deprivation in patients in the ICU include environmental disruption (eg, patient care including frequent neurologic assessments, labs collections, bright light, noise) and patient-specific biologic and cognitive factors (eg, pain, anxiety, stress, illness severity, mechanical ventilation requirement).[4,139] Sleep deprivation is very common among medical students, residents, and practicing physicians, leading to numerous negative personal and professional outcomes.[140,141] Implementation of healthy sleep practices should be encouraged and celebrated for patients and health care professionals. Structural, organizational, and individual-focused strategies to identify sleep-associated features of sleep deprivation and burnout should be initiated to educate and promote healthy sleep practices.

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Implications of Sleep Health Policy: Daylight Saving and School Start Times

By Karin G. Johnson, MD, FAAN, FAASM; Beth A. Malow, MD, MS, FAAN

SELECTED TOPICS IN NEUROLOGY PRACTICE

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ABSTRACT

Two proposed public policies, ending seasonal clock change with a transition to permanent Standard Time and moving middle school and high school start times later, are population-based initiatives to improve sleep health. Daylight Saving Time and early school start times are associated with reduced sleep duration and increased circadian misalignment, the effects of which impact not only long-term health outcomes including obesity, cerebrovascular and cardiovascular disease, and cancer, but also mental health, academics, workforce productivity, and safety outcomes. This article highlights studies that led to the endorsement of these public policies by multiple scientific and medical organizations. Neurologists should advocate at the state and federal levels and educate the population about the importance of sleep health.

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INTRODUCTION

Sleep and circadian health affect many outcomes including overall health, mood, cognition, and function. The American Heart Association changed Life's Simple 7 to Life's Essential 8 by adding sleep to its heart health measures.[1] The American Academy of Neurology (AAN) acknowledged the importance of sleep at its inaugural Brain Health Summit in 2022. Two public policies, ending seasonal clock change with a transition to permanent Standard Time (ST) and moving middle school and high school start times later, are population-based initiatives to improve sleep health and reduce structural disparities. This article starts with a review of circadian rhythms and how they are impacted by these two policies, followed by a discussion on the effects of Daylight Saving Time (DST) and school start times on health and mood and other broader implications for society (eg, education, work, motor vehicle crashes). The article concludes with a discussion of the current state of these policies.

SLEEP AND CIRCADIAN RHYTHMS

The four elements of healthy sleep are duration, quality, timing, and regularity. The disruption of any of these elements can affect health and function. Circadian rhythms affect all four elements of sleep by helping to anticipate daily changes in

KEY POINTS

- The four elements of healthy sleep are duration, quality, timing, and regularity.
- Circadian rhythms primarily align to solar time, or the time when the sun is overhead at noon.

the environment. The central clock in the brain sends signals to cells throughout the body to coordinate important functions, such as hormone secretion, heart function, metabolism, digestion, and sleep cycles. Circadian rhythms are also important for controlling cell growth and repair, clearing away toxic substances, and altering brain-cell connections to enhance memory and learning.[2]

Circadian rhythms primarily align to solar time, or the time when the sun is overhead at noon. In order for circadian rhythms to inform cells regarding the time of day, body clocks must align with the 24-hour day. Genetics, age, the timing of sunlight exposure, differences in ambient light levels such as living in the city versus the country, and medications all affect the timing of circadian rhythms. The circadian rhythms of approximately 90% of humans are slightly longer than 24 hours.[3] This can cause the rhythm to delay, or "run slow," if not reset daily. For most people, sunlight in the morning realigns the body clock back to 24 hours, keeping it in sync with the environment. Exposure to sunlight in the evening has the opposite effect; it delays circadian rhythms, causing the body to run later than 24 hours the next day. Artificial light can have similar effects, but body clocks respond most strongly to sunlight.

CLOCK CHANGES (DAYLIGHT SAVING TIME) AND CIRCADIAN RHYTHMS

People used to set their social clocks according to the position of the sun in the sky (solar time), leading to a 4-minute social clock difference for every 1° of longitude. In 1883, the United States legally established four time zones for the railroad industry. Ideal time zones have a uniform ST for locations with similar longitude. In an ideal time zone, the sun is overhead at noon at the time zone meridian (solar time) and all locations are within 30 minutes for ideal alignment. However, for political and economic reasons, the boundaries of time zones have been manipulated (FIGURE 1A). Locations on the western edges of

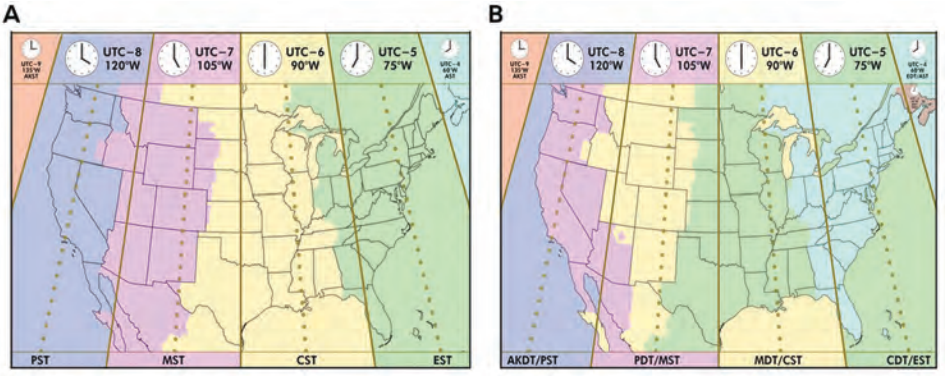

FIGURE 1

Time zones in the United States during Standard Time (*A*) and Daylight Saving Time (*B*). *Dotted lines* show the time zone meridians where the Sun is overhead at noon during Standard Time, and *solid lines* show the ideal time zone borders where the Sun is 30 minutes from noon during Standard Time.

AKDT = Alaska Daylight Time; AKST = Alaska Standard Time; CDT = Central Daylight Time; CST = Central Standard Time; EDT = Eastern Daylight Time; EST = Eastern Standard Time; MDT = Mountain Daylight Time; MST = Mountain Standard Time; PDT = Pacific Daylight Time; PST = Pacific Standard Time; UTC = Coordinated Universal Time

Image courtesy of Jay Pea.

most US time zones are misaligned from solar time by approximately 1 hour when on ST. The additional 1-hour delay during DST (during which clocks are advanced, an hour is "lost," and noon becomes 1 PM) increases misalignment with solar time (FIGURE 1B).

A clock time that is later than solar time, due to either DST or misaligned time zones, affects sleep and circadian rhythms in two ways. Because circadian time essentially remains aligned with solar time,[4] the social clock time shifts earlier compared to circadian time, forcing us to wake up before our bodies are ready. Additionally, later sunrises and sunsets shift circadian rhythms and sleep times later, widening the discrepancy between social time and circadian time even more than the 1-hour clock change. The degree of temporal misalignment can be objectively measured by social jet lag. Social jet lag is the difference between sleep timing on days with external influences (school or work days) and free days. Sleep timing on free days is determined by chronotype, which is the preference for sleep timing measured by the midpoint of sleep on free days.

Those with evening chronotypes (night owls) often prefer the later sunsets of DST because they align with their preferred wake time. However, people with evening chronotypes are most likely to be harmed by the loss of morning light in winter and later evening light in summer during DST, resulting in greater social jet lag and greater loss of sleep. This group is also most likely to benefit from the morning light that ST provides as it helps prevent further delay of their body rhythms, especially if school or work starts before 8:30 AM because body rhythms can block the ability to fall asleep early enough to get adequate sleep before the required wake time. On the other hand, those with morning chronotypes (morning larks) are typically able to maintain adequate sleep duration and regular sleep patterns without being affected by the social clock.

Evening chronotype is more common in adults than morning chronotype. Teens and young adults are most likely to have later sleep timing. For example, one study found that the average midpoint of sleep on free days peaks shortly before 5 AM in 20-year-olds, compared with before 3:30 AM after 32 years old.[5] Social jet lag peaks between 10 and 17 years old, presumably due to earlier middle and high school start times.[6]

The seasonal change to and from DST also has acute impacts on circadian rhythms. In the northern hemisphere, the spring switch from ST to DST leads to 1 hour less sleep time as clocks are set forward, which increases the misalignment between social and solar time. The fall switch from DST to ST adds 1 hour of sleep time as clocks are set back and the switch to ST improves the social and circadian

Percent of High School Students Sleeping at Least 8 Hours Per Night by School Time[a] TABLE 1

School start time	7:30 AM	7:35 AM	8:00 AM	8:05 AM	8:20 AM	8:35 AM	8:35 AM	8:35 AM	8:35 AM	8:55 AM
Sample size	333	446	1379	884	1353	902	1249	960	1407	459
Sleep >8 hours/ night	33.6%	44.2%	44.5%	49.7%	42.5%	49.8%	57.0%	58.9%	60.0%	66.2%

[a] Modified from Wahlstrom K, et al.[14] © 2014 University of Minnesota.

KEY POINTS

- Social jet lag is the difference between sleep timing on school or workdays and free days.
- Chronotype, or preference for sleep timing, is measured by the midpoint of sleep on free days.
- Social jet lag is greatest between ages 10 and 17 years.
- The spring clock transition from Standard Time to Daylight Saving Time is associated with more negative effects than the fall transition from Daylight Saving Time to Standard Time.
- Short-term effects of clock transitions do not equate to the long-term effects of permanent Daylight Saving Time or permanent Standard Time.

alignment. The spring change to DST results in 25 to 60 minutes of average sleep loss in the first days or weeks after the change,[7] but no average sleep is lost after the fall change to ST. However, evidence suggests that many people's sleep patterns never fully adjust to the later sunrises and sunsets of DST, leading to chronic sleep loss. This sleep loss is influenced by school and work start times.[8] For example, people without children who started work after 8:30 AM did not experience sleep loss compared to those with children or who began work before 8:30 AM, and those who started work before 7 AM were the most affected by sleep loss. Additionally, the amount of social jet lag[9] and the midpoint of sleep shifts later when sunrises and sunsets are later.[10]

LATER SCHOOL START TIMES AND CIRCADIAN RHYTHMS

As noted earlier, adolescents and young adults are more likely to have delayed circadian rhythms, resulting in evening chronotypes. This shift in circadian rhythms occurs with puberty and is related to two forces: a delay in natural melatonin release and a slowing of the buildup of chemicals that contribute to our drive to sleep (eg, adenosine). These forces result in an approximately 2-hour later bedtime.[11] The interaction between social schedule timing and circadian rhythm timing can be used to mitigate some of the negative impacts of circadian misalignment. Later school start times allow naturally sleep-delayed adolescents to sleep later on school days, which can reduce social jet lag, increase average sleep duration, and allow them to better match their body clocks to the social clock.

Teens are especially vulnerable to sleep loss because many middle and high schools start classes early, often before 8 AM and some as early as 7 AM. These early start times result from societal pressures, including the need to run two consecutive bus schedules, meaning that older children are transported to school followed by younger children, despite their delayed circadian rhythms. Other societal factors include teen availability for after-school childcare and sports programs. When factoring in time for getting ready and transportation to school in the morning, many teens do not get the 8 to 10 hours of sleep that is recommended for optimal health.[12] TABLE 1[13] shows the relationship between school start times and the percentage of high school students sleeping at least 8 hours per night. When considering circadian rhythms in relation to early school start times, recognizing that students may not be fully alert and ready to learn during first and second periods based on their chronotype is also important.

EVALUATING THE EFFECTS OF TIME POLICY

Most studies of DST evaluate the short-term effects of the spring and fall transitions by comparing periods before and after clock changes. These studies should not be used to determine the long-term impacts of permanent time policy. Instead, several study types provide data to support the expected long-term effects of permanent DST versus permanent ST: studies of natural experiments, position within time zones, and sleep and circadian disruption. Natural experiments compare the same or nearby locations on DST versus ST, such as when the United States tried implementing permanent DST in 1974 or when Russia did so from 2011 to 2014, with other periods. Other opportunities for data collection include when Indiana and Australia adjusted their clock times, or comparing Arizona and Hawaii, which are on permanent ST, with other states. However, few studies have compared the effects throughout all seasons of the year in the same location.

Evaluating Long-Term Effects of Daylight Saving Time

Borisenkov and colleagues[9] provided data from the only year-round natural experiment of permanent DST. The study used self-reported sleep data from school students in northern regions of Russia collected during seasonal DST from 2009 to 2011, permanent DST from 2011 to 2014, and permanent ST from 2015 to 2016. Average weekly sleep duration was the lowest during permanent ST (7.34 ± 1.31 hours) versus permanent DST (7.40 ± 1.21 hours) and seasonal DST (7.69 ± 1.18 hours, P <0.001). The longer duration during DST was due to a larger amount of social jet lag and later rise time during permanent DST. More adolescents (7% to 8%) had 1 to 2 hours and 17% had 2 or more hours of social jet lag during permanent DST than during either seasonal DST or permanent ST. Despite an increase in sleep, permanent DST was associated with an increase in seasonal depression suggesting that, at least in teenagers, quality and alignment of sleep may be more important than average weekly self-reported sleep duration.

Some people believe that the only impact of DST is from the clock transition itself because that is when they notice a sudden change in sleep, alertness, cognition, and mood. One may also think that any chronic sleep loss would be too minimal to have significant impacts. This study highlights how despite no overall changes in weekly average sleep duration during permanent DST, many more adolescents were impacted by a loss of sleep regularity with increases in social jet lag.[9] This study also contradicts a common misconception that mood would improve with more light exposure at the end of the day. Instead, it supports the known connections between mood disorders and light exposure and circadian misalignment, namely, that morning light improves mood and evening light and more delayed circadian rhythms can worsen depression and other mental health disorders.[14]

A second way to study the long-term effects of later clock time is to compare locations within the same time zone that have different sunrise and sunset times. By comparing westerly to easterly locations that have a 1-hour difference in clock time, estimates of the effect of the 1-hour difference between DST and ST clock times can be made. Other methods for studying the effect of clock misalignment include linearly adjusting for distance from the time zone meridian or comparing locations with a sun time more or less than 30 minutes from the time zone meridian. Because DST increases the percentage of people with social jet lag and

Short-term Societal Effects of Standard Time to Daylight Saving Time Transitions TABLE 2

- Sleepy students
- Increased stock market volatility[28]
- Increased workplace injuries[29]
- Increased fatal motor vehicle crashes[30,31]
- Slower marathon running times[32]
- Increased activity levels in some countries[27]
- Reduced evening robberies[24]
- More energy-efficient lighting[25]

KEY POINT

- Seasonal depression rates are highest during permanent Daylight Saving Time and lowest during permanent Standard Time.

evening chronotype, studying the outcomes associated with these markers of delayed circadian rhythms is also informative about the impacts of DST. Data from later school start time studies can also support the importance of improved social and circadian alignment.[16]

EFFECTS OF DAYLIGHT SAVING TIME ON HEALTH AND PERFORMANCE

In the days after the spring clock change from ST to DST, studies have found an increased risk of atrial fibrillation, heart attacks, depression, suicide attempts, emergency department visits, failure of in vitro fertilization, mortality, and stroke.[16,17] Missed medical appointments and medical errors also increase after the ST-to-DST transition and may impact health.[18,19] When clocks transition back to ST in the fall, most of these negative effects on health are not seen.[20] Position-in-time-zone studies have provided the most data on the long-term effects of later sunrises and sunsets, showing increased risks of obesity, diabetes, cardiovascular disease, and some cancers.[8,21,22]

Giuntella and colleagues[8] evaluated the effect of position in a time zone on health and workplace productivity outcomes. They found that 1-hour later sunrise and sunset times were associated with a 10% increased risk of obesity, a 19% increased risk of heart attack, a 16% increased risk of heart disease, and a 5% increased risk of type 2 diabetes. This study estimated that the increased risks of these problems alone would lead to over $2.3 billion per year in increased health care expenses if permanent DST were adopted.[8] Additionally, they estimated 4.4 million days of lost work productivity costing over $600 million annually in the United States. They also found that wages were 3% lower on the western edges of time zones.[8]

Many of the strongest arguments for permanent DST are the benefits to the economy from an increase in retail and recreational activities, especially in the fall and spring when sunsets are later during DST. What the economic evaluation often overlooks is the effects on the overall workforce. This study found that DST would decrease worker productivity due to tardiness or absences and increased health problems,[8] while other studies showed that sleep and circadian disruption lead to billions of dollars of productivity losses[23]; affect concentration, memory formation, and decision making[24]; lead to increases in surfing the internet at work (cyberloafing)[25] and workplace injuries[26]; and decreases in academic performance.[27]

EFFECTS OF DAYLIGHT SAVING TIME ON SOCIETY

The alleged benefits of DST on society derive from the shift of light from before typical work and school time to after, allowing more time for recreational and economic activities as well as a reduction in energy costs for electrical lighting. The overall long-term impacts of DST balance the positive effects of later evening light on activity and safety and the negative effects of later light exposure on sleep and circadian disruption and loss of morning light. The short-term effects of the sudden shifts in clock time in the spring and fall on societal outcomes (TABLE 2) do not necessarily predict the long-term effects of permanent DST or ST.

Some outcomes, such as reductions in crime[33] and energy use[34] and an increase in consumer sales,[35] that may see a short-term boost with more evening light in the spring and fall may have the opposite effect in the winter and summer for several reasons. First, the circadian impacts of later sunrises and sunsets are more likely to be harmful in the winter and summer at the extremes of the photoperiod

(day length). If permanent DST were enacted, sunrise would occur after 8 AM for 2 to 4 months in the United States (TABLE 3 and FIGURE 2), depriving most people of critical morning light needed for optimizing alertness, cognitive function, reaction time, and decision making, with negative effects on productivity and safety outcomes. Second, the potential benefits of later sunrises and sunsets on recreational activity, energy use, and spending may be mitigated by heat in the summer and cold in the winter. The effects of DST can be modulated by latitude, climate, and culture. For example, after the shift to DST, a short-term increase in children's daily physical activity was seen in Northern Europe, but no statistical change was seen in the United States and a decrease was seen in Brazil.[36]

Some of the short-term economic boosts may not be considered favorable by the public. A short-term study by JP Morgan compared Los Angeles, California, before and after time changes to Phoenix, Arizona, which remains on permanent ST.[31] The study found that Los Angelenos had relatively higher credit card spending on retail purchases during DST; however, utility bills, gasoline, and health care expenditures also increased during DST. This finding is consistent with another study in Indiana that found 1% higher residential energy bills during seasonal DST compared to permanent ST primarily due to increased heating and air conditioning use during DST.[37]

Long-term, year-round energy data are limited. Although small overall energy savings were seen in the US Department of Energy studies of permanent DST in 1974[38] and extended DST (when DST was extended from April–October to March–November) in 2007,[34] these data may not reflect current energy consumption. First, lighting has become more energy efficient. Second, the use of heating, air conditioning, and electronics has increased. Finally, the 1974 data may have been impacted by energy restrictions in place

Winter Sunrise Times with Permanent Daylight Saving Time[a] TABLE 3

City	Sunrise after 8 AM		Months with sunrise after 8 AM	Latest sunrise
	First Day	Last Day		
Boston, MA	Dec 6	Jan 31	1.9 months	8:14 AM
San Antonio, TX	Nov 16	Mar 2	3.5 months	8:30 AM
San Francisco, CA	Nov 24	Feb 15	2.8 months	8:26 AM
Tallahassee, FL	Nov 11	Mar 5	3.8 months	8:36 AM
Atlanta, GA	Nov 4	Mar 7	4.1 months	8:44 AM
Chattanooga, TN	Oct 29	Mar 10	4.4 months	8:51 AM
Minneapolis, MN	Nov 7	Feb 24	3.6 months	8:52 AM
Seattle, WA	Nov 5	Feb 24	3.7 months	8:58 AM
Detroit, MI	Oct 27	Mar 6	4.3 months	9:02 AM
Indianapolis, IN	Oct 19	Mar 13	4.8 months	9:07 AM

[a] Data from International Alliance for Natural Time, savestandardtime.com/chart.

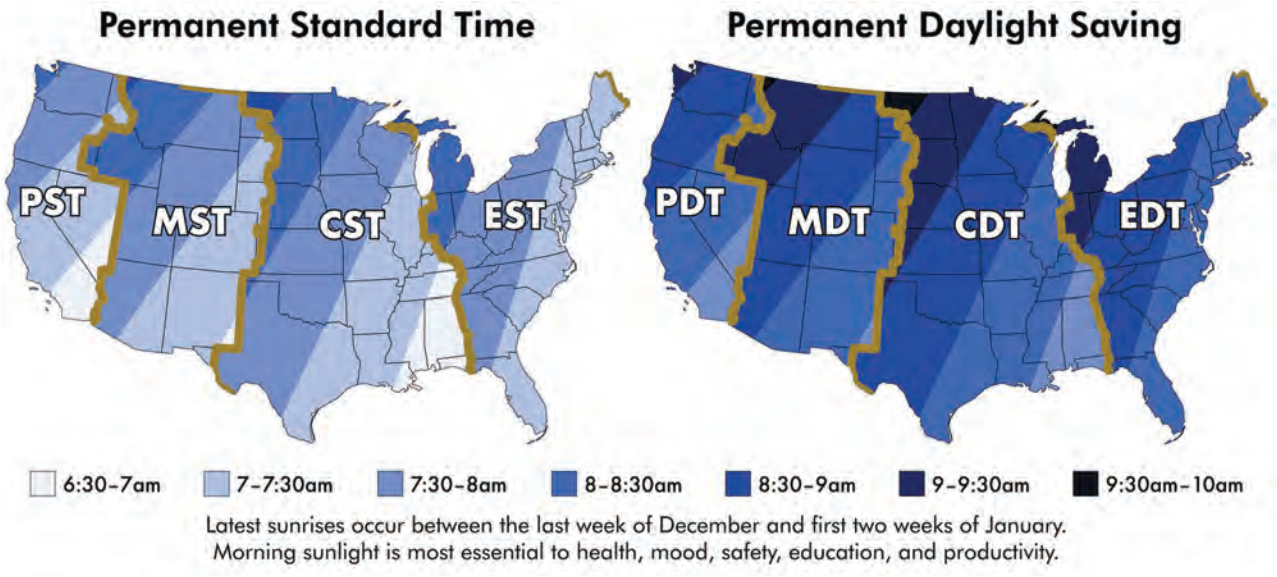

FIGURE 2
Latest sunrise times on permanent Standard Time and Daylight Saving Time.
CDT = Central Daylight Time; CST = Central Standard Time; EDT = Eastern Daylight Time; EST = Eastern Standard Time; MDT = Mountain Daylight Time; MST = Mountain Standard Time; PDT = Pacific Daylight Time; PST = Pacific Standard Time.
Image courtesy of Jay Pea.

during the oil crisis. Year-round studies comparing Arizona to locations with similar climates would help establish whether DST contributes to increased energy consumption between spring and fall but would not reflect changes in winter when both already use ST or reflect heating costs in colder locations.

Long-Term Effects of Later Sunrise and Sunset on Safety

Gentry and colleagues[39] compared 12 years of fatal motor vehicle crashes in the United States for those located in their ideal time zone (within 30 minutes or 7.5° of the time zone meridian) with eccentric locations of more than 30 minutes delay from solar time (FIGURE 3). They found that eccentric regions had 20.8% more fatal motor vehicle crashes. This study highlights the importance for locations to be in their appropriate time zone as well as remain on ST.

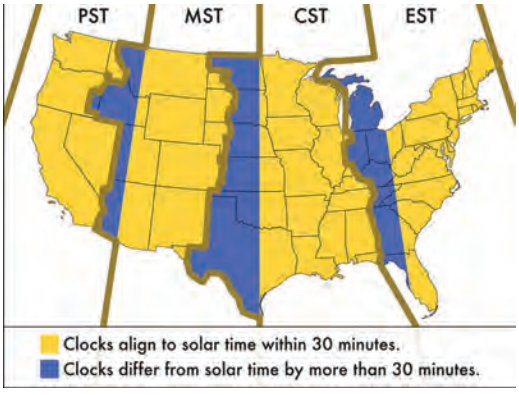

FIGURE 3
Eccentric time zones.
CST = Central Standard Time; EST = Eastern Standard Time; MST = Mountain Standard Time; PST = Pacific Standard Time
Image courtesy of Jay Pea.

LATER SCHOOL START TIMES

School start times impact students,[16] parents,[40] and teachers.[41] Later school start times show improved sleep duration and regularity and

multiple outcomes including health, mood disorders, behavior problems, brain development, academics, delinquency, risk-taking behavior, judgment, and decision-making ability. Students with later school start times have extended sleep duration; increased alertness and performance; improved physical and mental health, learning, attendance, graduation rates, and overall well-being; and fewer car crashes.[42] While a common concern about adopting later school start times is the impact on afterschool activities including sports, beneficial effects of sleep on sports performance and a reduction of sports-related injuries in adolescents have been found in some school districts even if practice times are shorter.[43,44]

Moving elementary school times earlier does not impact outcomes, which is important because of the busing demands of moving middle and high school start times later.[45] Older adolescents and young adults are also affected by the earlier start times of their college classes, with shorter sleep duration and lower grades.[46] A separate study showed that college students who got less sleep had lower grades.[47]

Effect of Later School Start Times on Sleep, Academics, Safety, and Mental Health

Wahlstrom[14] evaluated over 9000 students at eight public high schools in three states by comparing school start times over 3 years. Later school start times allowed more than 60% of students to obtain at least 8 hours of sleep on school nights. Students with school start times of 8:35 AM or later had higher grades, better state and national achievement test performance, higher attendance rates, and less tardiness. The study also found that car crashes involving teen drivers decreased by 70% when one school shifted its start times from 7:35 AM to 8:55 AM.[14] Finally, they found that students getting less than 8 hours of sleep were more likely to have depression symptoms, use caffeine more often, and use illicit drugs, cigarettes, and alcohol.

In general, the literature provides strong evidence that middle and high school start times after 8:30 AM are associated with improvements in sleep, attention, mood, and academic outcomes, and reductions in absences, tardiness, and risk-taking behaviors, all of which led the American Academy of Pediatrics,[42] American Association of Sleep Medicine,[48] and others to endorse later school start times. Another study performed in a school district with very early middle and high school start times (7:20 AM) found associations between short sleep duration and feeling hopeless, suicidal ideation, suicide attempts, and substance use.[49]

INTERACTION BETWEEN LATER SCHOOL START TIMES AND DAYLIGHT SAVING TIME

Given the benefits of later school start times, some have suggested the switch to permanent DST, moving work and school times later. While this solution would help mitigate the adverse effects of DST, later sunsets and sunrises shift the circadian rhythms of people with evening chronotype by more than 1 hour (increasing social jet lag), so ST provides the best overall circadian alignment. Additionally, moving work and school later would remove the benefit of more time at the end of the day in the sunlight, which is a main argument for DST. On the other hand, the combination of permanent ST and later school start times

KEY POINTS

- **Motor vehicle crash rates are higher in locations with later sunrises and sunsets.**
- **Later school start times are associated with higher attendance, higher grades, and better test scores.**

would allow students to have the best alignment between their circadian rhythms and social schedule.

DAYLIGHT SAVING TIME, SCHOOL START TIMES, AND SLEEP HEALTH DISPARITIES

Public health policies are often used to help lessen the effect of structural disparities. As discussed earlier, social factors such as work and school start times impact the sleep and circadian disruption caused by later sunrises and sunsets and early school or work start times.

Two studies illustrate how permanent ST and later school start times can help mitigate sleep health disparities. Gaski and colleagues[50] evaluated mean Scholastic Aptitude Test (SAT) scores from 350 Indiana public high schools over a 10-year period (1997 to 2006) by comparing regions that followed seasonal DST with those on permanent ST. Mean SAT scores were 16 points lower on average in seasonal DST regions compared with ST regions. This effect was modulated by income, with students from the lowest-income families having the largest drop in scores. Edwards[51] used data on all middle school students in Wake County, North Carolina from 1999 to 2006 to identify the causal effect of daily start times on academic performance. During this time, the school population grew from 20,530 students enrolled in 22 middle schools to 27,686 students enrolled in 28 middle schools, with many schools changing to earlier or later start times. Later-starting students had higher test scores in math and reading. This increase in test scores was attributed to increased sleep, as well as factors such as fewer absences and more time at home with their parents (eg, potentially more time doing homework and less time watching television). The effect of later start times had the strongest impact on students with test scores on the lower end of the distribution (using a quartile regression model).

These studies highlight the structural disparities associated with sleep health public policies. The importance of socioeconomic status as a structural determinant of sleep health and its association with racial disparities in sleep are becoming increasingly clear.[48] A study of late adolescents, for example, found that socioeconomic status was a moderator of the relationship between sleep and developmental outcomes.[49] Sleep disparities may influence some health disparities; one example was a 50% higher rate of liver cancer in non-Hispanic Black people and non-Hispanic Asian, Pacific Islander, American Indian, and Alaskan Native people exposed to later sunrise and sunset times.[22]

The effect of misaligned clock time may be even greater in developing countries. A non-peer-reviewed study evaluating 3 million people in developing countries also found that children from lower-income families were less likely to complete primary and middle school if they were exposed to later sunrises and sunsets such as one would experience on permanent DST.[54] Over the course of a child's education, the later sun times were associated with an average of 9 fewer months of schooling.[54]

PERMANENT STANDARD TIME ADVOCACY

Over the last decade, action at the local, state, and national levels in support of ending time change and moving school start times later has increased. Approximately 70% of people want to end seasonal clock

changes.[55] About 60% of the world uses permanent ST, with Mexico being the most recent country to adopt it in 2022. On the other hand, despite several countries briefly adopting permanent DST, including the United States (twice, most recently in 1974), it has always been abandoned. Before the 1966 Uniform Time Act, states independently decided on time policy, which caused issues with communication, economics, and transportation.

Prior to position statements from the Society of Research in Biological Rhythms (2019)[56] and the American Academy of Sleep Medicine (2020)[16] in support of permanent ST, about 15 states passed legislation that would enact permanent DST if allowed by the federal government, as it is currently federally prohibited. Most of these bills were passed without discussion of the health implications. In March 2022, the US Senate passed the Sunshine Protection Act which, if enacted, would require all states except Arizona and Hawaii to adopt permanent DST; however, it failed to pass the US House of Representatives. The act was reintroduced in 2023. With increasing action from Save Standard Time, a nonprofit organization supporting permanent ST, and over 90 scientific and medical societies (including recent endorsements by the American Medical Association,[57] the AAN, and the Sleep Research Society[58]) and religious and educational organizations, more state-level bills for permanent DST have failed to pass and more permanent ST bills have been sponsored. While a federal bill would be preferable to reduce economic and transportation confusion, the passage of state bills, even if they are contingent on similar legislation in nearby states, is important to show support for permanent ST given the state-level permanent DST bills that have previously passed.

LATER SCHOOL START TIME ADVOCACY

Later school start time advocacy to start middle and high schools no earlier than 8:30 AM has primarily occurred on a local level with individual schools or school districts often led by Start School Later chapters which, as of May 2023, are active in four countries, 33 states, and Washington, DC. However, state and federal governments can still have an important role. In 2022, California became the first state to mandate that high schools start no earlier than 8:30 AM for most communities followed by Florida in 2023. These larger-scale mandates are important because they help ensure that structural disparities are improved for all children. They also help mitigate some of the concerns about later school start times, including aligning after-school sports. The most successful communities have involved all stakeholders as changes to before-school and after-school care and activities are needed if work schedules do not also shift.[40]

CONCLUSION

Permanent ST and later school start times are public health measures that can lead to widespread benefits to sleep and circadian health. Improvements in circadian alignment and sleep duration will benefit a range of health outcomes. Both advocacy efforts are an opportunity to engage and educate the public on the science and importance of sleep health and circadian rhythms in daily life.

KEY POINTS

- The American Academy of Neurology (AAN) and over 90 medical, scientific, safety, education, and religious groups have endorsed permanent Standard Time.
- Middle schools and high schools should start classes after 8:30 AM.

USEFUL WEBSITES

SAVE STANDARD TIME
This website includes information about the effects of Daylight Saving Time, charts to determine sunrise and sunset times, a list of endorsements, and other information and links to assist with advocacy.

savestandardtime.com

THE SCIENCE OF CLOCK CHANGE
A series of 12 short educational videos on the history and effects of time change, hosted by Save Standard Time.

youtube.com/@SaveStandard

START SCHOOL LATER
This website has a comprehensive list of resources for learning about and advocating for later school start times.

startschoollater.net

TAKE ACTION
Send prewritten emails to state and federal legislators, using the forms available from the American Academy of Sleep Medicine or resistbot by texting SST to 50409.

aasm.org/advocacy/take-action

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Postreading Self-Assessment and CME Test

By D. Joanne Lynn, MD, FAAN; Allyson R. Zazulia, MD

SLEEP NEUROLOGY

The *Continuum* Postreading Self-Assessment and CME Test is an integral part of the issue that is intended to stimulate thought and help participants assess general understanding of the material presented in this issue. The Postreading Self-Assessment and CME Test is also approved by the American Board of Psychiatry and Neurology (ABPN) to meet the Lifelong Learning (CME), Self-Assessment (SA) (part 2) component for Continuing Certification (CC).

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ARTICLE 1: CLINICAL NEUROBIOLOGY OF SLEEP AND WAKEFULNESS

1 The primary mechanism by which caffeine exerts wakefulness is through antagonism of which of the following receptors?

A adenosine
B γ-aminobutyric acid (GABA)
C dopamine
D glutamate
E serotonin

2 Neurons in which of the following structures have been implicated in the coordination of slow-wave sleep?

A claustrum
B globus pallidus
C habenula
D insula
E putamen

3 Light input from the retinohypothalamic tract is received by what nucleus to entrain circadian timing to environmental light-dark cycles?

A globus pallidus
B medial geniculate nucleus
C nucleus accumbens
D suprachiasmatic nucleus
E thalamic reticular nucleus

ARTICLE 2: CLINICAL EVALUATION OF THE SLEEPY AND SLEEPLESS PATIENT

4 The use of which of the following medications most commonly induces rapid eye movement (REM) sleep behavior disorder?

A antidepressants
B corticosteroids
C dopamine agonists
D opioid analgesics
E stimulants

5 Which of the following physical exam findings is a risk factor for sleep-related breathing disorders?

A complete soft palate visualization with mouth opening and tongue protrusion
B micrognathia
C neck circumference less than 43 cm (17 in)
D peripheral facial palsy
E tonsillar absence

6 A 34-year-old woman is seen in the clinic for difficulty falling asleep. She reports having uncomfortable sensations in her legs when she lies down at night. She has a feeling of needing to move her legs, which is relieved only by getting up and walking around. According to her bed partner, she does not snore, stop breathing, or have rhythmic movements of her legs during sleep. Physical examination is unremarkable. Which of the following polysomnographic tests should be recommended to this patient?

A in-home unattended polysomnography
B in-laboratory attended polysomnography
C maintenance of wakefulness test
D multiple sleep latency test
E no polysomnographic testing should be recommended

ARTICLE 3: CENTRAL DISORDERS OF HYPERSOMNOLENCE

7 Which of the following treatments for excessive daytime sleepiness exerts its primary mechanism of action through the histamine H3 receptor system?

A clarithromycin
B modafinil
C pitolisant
D sodium oxybate
E solriamfetol

8 Narcolepsy type 1 is caused by a loss of hypothalamic neurons that produce which of the following?

A γ-aminobutyric acid (GABA)
B dopamine
C leptin
D melatonin
E orexin (hypocretin)

9 In addition to narcolepsy type 1, cataplexy can also be seen in which of the following disorders?

A autoimmune encephalitis
B cystic fibrosis
C fragile X syndrome
D Klinefelter syndrome
E sleep terror syndrome

ARTICLE 4: OBSTRUCTIVE SLEEP APNEA

10 A patient with obstructive sleep apnea returns to the clinic with continued daytime somnolence 6 weeks after being started on autoadjusting positive airway pressure (APAP). Adherence data show an average use of 6 hours 20 minutes with a high device-estimated apnea-hypopnea index. Which of the following is the next best step in management?

A add home carbon dioxide monitoring
B assess for mask leak
C encourage better adherence to positive airway pressure use
D reduce level of air pressure delivered
E switch from APAP to continuous positive airway pressure (CPAP)

11 Which of the following treatments is most appropriate for children with obstructive sleep apnea?

A hypoglossal nerve stimulation
B mandibular advancement devices
C orthodontic treatment
D positive airway pressure
E tonsillectomy and adenoidectomy

12 Which of the following medications may be beneficial for symptomatic rapid eye movement (REM)-related respiratory events?

A carbonic anhydrase inhibitors
B hormone replacement therapy
C leukotriene antagonists
D medical cannabis
E tricyclic antidepressants

ARTICLE 5: REM SLEEP BEHAVIOR DISORDER AND OTHER REM PARASOMNIAS

13 Which of the following features is more typical of non–rapid eye movement (REM) parasomnia than REM sleep behavior disorder?

A easily awakened by others
B eyes closed during the event
C most occur in second half of the sleep period
D no awareness of environment
E sleepwalking outside of the bedroom

14 Which of the following is considered the core polysomnographic feature of rapid eye movement (REM) sleep behavior disorder?

A desynchronized alpha and theta EEG background
B periodic limb movements and delta background
C recurrent nightmares
D REM sleep without atonia
E sleep-related vocalization

15 Lesions in which of the following sites may interfere with rapid eye movement (REM) sleep and the mechanisms that preserve REM atonia?

A hypothalamic preoptic nucleus
B medial geniculate nuclei
C pulvinar
D sublateral dorsal nucleus
E ventral anterior nucleus of the thalamus

16 Which of the following medications is most likely to induce or worsen rapid eye movement (REM) sleep behavior disorder?

A bupropion
B diazepam
C methylphenidate
D tramadol
E venlafaxine

17 Which of the following medications is the first-line pharmacologic treatment for nightmare disorder and posttraumatic stress disorder–associated nightmares?

A atenolol
B clonazepam
C fluoxetine
D melatonin
E prazosin

ARTICLE 6: NON–REM SLEEP PARASOMNIAS

18 **A 28-year-old man has had multiple events associated with intense fearfulness, screaming, tachycardia, and diaphoresis during sleep. During one episode, he jumped out of bed and locked himself in the bathroom. After the events, he remembers a vague sense of fear but has no recollection of a particular dream or what he was afraid of. Which of the following sleep disorders is most likely in this patient?**

A confusional arousal
B nightmare
C rapid eye movement (REM) sleep behavior disorder
D sleep terror
E sleepwalking

19 **A 16-year-old girl is seen in clinic after an event during sleep where she got out of bed, moved the furniture in her room, and went back to bed. She had no memory of the event in the morning. She had stayed up late the night before. She had a history of sleepwalking during her elementary school years. Which of the following is the next best step in management?**

A order polysomnography
B provide safety counseling
C start daily tricyclic antidepressant
D trial benzodiazepine therapy
E use bedtime waist belt restraint

20 **Which of the following electroencephalographic features is associated with the behavioral events of non–rapid eye movement (non-REM) parasomnias?**

A cortical arousals
B periodic frontal epileptiform discharges
C regionally increased delta activity
D REM intrusions during stage N3 sleep
E sinusoidal alpha rhythm

21 **Which of the following medications is associated with an increased likelihood of non–rapid eye movement (non-REM) parasomnias?**

A clonazepam
B clonidine
C gabapentin
D melatonin
E zolpidem

22 **Which of the following medications is most strongly associated with the phenomenon of augmentation in the treatment of restless legs syndrome?**

A ferric carboxymaltose
B gabapentin
C pramipexole
D pregabalin
E tramadol

23 **Which of the following medications commonly worsens restless legs syndrome?**

A clopidogrel
B diphenhydramine
C lisinopril
D metformin
E metoprolol

24 **Evaluation of restless legs syndrome should include which of the following blood tests?**

A albumin
B copper
C ferritin
D hemoglobin
E iron

25 **Treatment of sleep disorders with which of these medications may be associated with the emergence of impulse control disorders such as excessive spending or gambling?**

A buprenorphine hydrogen chloride/naloxone
B carbidopa/levodopa
C gabapentin
D magnesium
E rotigotine

ARTICLE 8: CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

26 Which of the following management strategies is most appropriate for a completely blind individual with non-24-hour sleep-wake rhythm disorder?

A cognitive behavioral therapy
B late-night food intake
C regular late afternoon naps
D scheduled melatonin
E timed light exposure

27 Which of the following brain structures functions as the central pacemaker of circadian rhythms in mammals?

A anterior pituitary gland
B periventricular zone
C pineal gland
D preoptic area
E suprachiasmatic nucleus

28 Which of the following wavelengths of visible light most greatly inhibits melatonin secretion?

A blue
B green
C magenta
D red
E yellow

29 Which of the following observations of time best aligns environmental cues with the internal clock?

A permanent Daylight Saving Time
B permanent Standard Time
C setting clocks back by 1 hour in the spring and forward by 1 hour in the fall
D setting clocks forward by 1 hour in the spring and back by 1 hour in the fall

30 The diagnosis of insomnia disorders requires which of the following?

A actigraphy
B history alone
C polysomnography
D sleep-onset latency recording
E video sleep recording

31 Most US Food and Drug Administration (FDA)-approved medications for insomnia work via modulation of which neurotransmitter system?

A γ-aminobutyric acid (GABA)
B dopamine
C histamine
D norepinephrine
E orexin (hypocretin)

32 Which of the following medications for insomnia belongs to the class of dual orexin receptor antagonists?

A eszopiclone
B mirtazapine
C ramelteon
D suvorexant
E zaleplon

33 Which of the following medications for the treatment of insomnia works at least partially through histamine antagonism?

A gabapentin
B melatonin
C mirtazapine
D triazolam
E zolpidem

ARTICLE 10: SLEEP DISORDERS IN PATIENTS WITH NEUROLOGIC DISEASE

34 Which of the following sleep disorders may increase the risk of stroke through the development of cardiac arrhythmia?

A insomnia
B obstructive sleep apnea
C periodic limb movement disorder
D restless legs syndrome
E shift work sleep-wake disorder

35 Narcolepsy is a core clinical feature in the diagnostic criteria for which of the following neurologic disorders?

A multiple system atrophy
B myasthenia gravis
C myotonic dystrophy
D neuromyelitis optica spectrum disorder
E stiff person syndrome

36 A 67-year-old woman reports chronic daily headaches for the past year. Her headaches are exclusively nocturnal, waking her up from sleep every night around midnight and lasting 30 minutes to 2 hours. She has no major medical problems and takes no regular medications. Clinical examination and laboratory and imaging studies are unremarkable. Which of the following abortive treatments is most appropriate for this patient?

A antiemetic
B caffeine
C calcitonin gene-related peptide antagonist
D dihydroergotamine
E triptan

ARTICLE 11: SLEEP DISORDERS IN CHILDHOOD

37 Which of the following is a potential complication of positive airway pressure therapy in children?

A asthma
B gastric reflux
C hypertension
D midface hypoplasia
E pulmonary hypertension

38 Pediatric narcolepsy type 1 is associated with which of the following conditions?

A anorexia
B epilepsy
C iron deficiency anemia
D precocious puberty
E sudden infant death syndrome

ARTICLE 12: SLEEP DEPRIVATION AND ITS CONSEQUENCES

39 Acute sleep deprivation may result in short-term remission of which of the following psychiatric disorders?

A anxiety
B delirium
C major depression
D mania in bipolar disorder
E psychosis

40 In which of the following ways may chronic sleep deprivation contribute to cardiovascular disease?

A decrease in heart rate
B enhancement of the physiologic nocturnal dip in blood pressure during non-rapid eye movement (non-REM) sleep
C impairment of endothelium-dependent vasodilation
D reduction in evening cortisol concentration
E suppression of the sympathetic nervous system

Postreading Self-Assessment and CME Test—Preferred Responses

By D. Joanne Lynn, MD, FAAN; Allyson R. Zazulia, MD

SLEEP NEUROLOGY

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

US PARTICIPANTS: Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at continpub.com/CME, participants may earn up to 20 *AMA PRA Category 1 Credits*™ toward SA-CME. US participants have up to 3 years from the date of publication online to earn SA-CME credits.

CANADIAN PARTICIPANTS: This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the University of Calgary Office of Continuing Medical Education and Professional Development. Refer to the CME tab on ContinuumJournal.com for dates of accreditation. Canadian participants should visit MAINPORT (mainport.org) to record learning and outcomes. Canadian participants can claim a maximum of 20 hours per issue (credits are automatically calculated).

ARTICLE 1: CLINICAL NEUROBIOLOGY OF SLEEP AND WAKEFULNESS

1 The preferred response is **A (adenosine).** The main target of caffeine antagonism is the adenosine receptor. A1 receptors are found at high levels in the brain, especially in the cortex, hippocampus, and thalamus. Activation of A_1 receptors promotes sleep by inhibiting wake-active neurons of the forebrain and the ascending reticular activation system. Caffeine antagonism of the A_1 receptors promotes wakefulness. For more information, refer to **page 1017** of the *Continuum* article "Clinical Neurobiology of Sleep and Wakefulness."

2 The preferred response is **A (claustrum).** Neurons in the claustrum project over large cortical regions and show the highest activity during slow-wave sleep. Evidence implicates the claustrum as the coordinator of slow-wave sleep. In addition, disruptions in claustrum circuitry have been associated with insomnia, suggesting a role in sleep initiation. For more information, refer to **page 1021** of the *Continuum* article "Clinical Neurobiology of Sleep and Wakefulness."

3 The preferred response is **D (suprachiasmatic nucleus).** The suprachiasmatic nucleus receives light input from the retinohypothalamic tract with resultant entrainment of circadian timing to environmental light-dark cycles and functions as a circadian pacemaker. The retinohypothalamic tract also projects to the habenula, subparaventricular zone, ventrolateral preoptic nucleus, and lateral geniculate nucleus. For more information, refer to **page 1021** of the *Continuum* article "Clinical Neurobiology of Sleep and Wakefulness."

ARTICLE 2: CLINICAL EVALUATION OF THE SLEEPY AND SLEEPLESS PATIENT

4 The preferred response is **A (antidepressants).** Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants are the most commonly used medications that trigger rapid eye movement (REM) sleep behavior disorder. Other antidepressants, including venlafaxine, mirtazapine, and monoamine oxidase inhibitors (MAOIs), may also induce the condition. For more information, refer to **page 1035** of the *Continuum* article "Clinical Evaluation of the Sleepy and Sleepless Patient."

5 The preferred response is **B (micrognathia).** Anatomic risk factors for sleep-related breathing disorders are those that increase the degree of upper airway crowding, including obesity or large neck circumference, and midline facial anomalies such as micrognathia, retrognathia, macroglossia, high-arched palate, and cleft lip or palate. For more information, refer to **page 1035** of the *Continuum* article "Clinical Evaluation of the Sleepy and Sleepless Patient."

6 The preferred response is **E (no polysomnographic testing should be recommended).** This patient has symptoms consistent with restless legs syndrome. Since there is low suspicion for another sleep disorder, polysomnographic evaluation is not necessary. For more information, refer to **page 1039** of the *Continuum* article "Clinical Evaluation of the Sleepy and Sleepless Patient."

ARTICLE 3: CENTRAL DISORDERS OF HYPERSOMNOLENCE

7 The preferred response is **C (pitolisant).** Pitolisant is a histamine H3 receptor inverse agonist that can improve sleepiness and reduce cataplexy in patients with narcolepsy. For more information, refer to **page 1061** of the *Continuum* article "Central Disorders of Hypersomnolence."

8 The preferred response is **E (orexin [hypocretin]).** Narcolepsy type 1 appears to be caused by the selective loss of orexin (hypocretin)-producing neurons in the hypothalamus. Orexin (hypocretin) is a peptide that promotes wakefulness. An immune-mediated etiology is supported by the association with specific human leukocyte antigen alleles. For more information, refer to **page 1052** of the *Continuum* article "Central Disorders of Hypersomnolence."

9 The preferred response is **A (autoimmune encephalitis).** Excessive daytime somnolence with or without cataplexy can be seen in disorders that cause structural lesions of the hypothalamus such as trauma, infection, or inflammation including in association with autoimmune encephalitis, especially with anti-Ma2 autoantibodies. Cataplexy has also been associated with pediatric genetic syndromes such as Niemann-Pick type C disease, Angelman syndrome, Prader-Willi syndrome, and myotonic dystrophy. For more information, refer to **page 1053** of the *Continuum* article "Central Disorders of Hypersomnolence."

ARTICLE 4: OBSTRUCTIVE SLEEP APNEA

10 The preferred response is **B (assess for mask leak).** This patient with obstructive sleep apnea remains symptomatic and has a high residual apnea-hypopnea index despite good adherence to positive airway pressure therapy. Mask leaks can result in inadequate treatment response related to both sleep arousals from the leak itself and from subtherapeutic pressure delivery; thus, mask fitting is the most appropriate next step in the management of this patient. For more information, refer to **page 1084** of the *Continuum* article "Obstructive Sleep Apnea."

11 The preferred response is **E (tonsillectomy and adenoidectomy).** In children, the most common cause of obstructive sleep apnea is blockage of the airway by enlarged tonsils and adenoids. Thus, the most appropriate treatment for these children is tonsillectomy and adenoidectomy. For more information, refer to **page 1087** of the *Continuum* article "Obstructive Sleep Apnea."

12 The preferred response is **E (tricyclic antidepressants).** Disordered breathing events that predominantly or exclusively manifest during rapid eye movement (REM) sleep and produce clinical symptoms may respond to REM-suppressing medications such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). For more information, refer to **page 1088** of the *Continuum* article "Obstructive Sleep Apnea."

ARTICLE 5: REM SLEEP BEHAVIOR DISORDER AND OTHER REM PARASOMNIAS

13 The preferred response is **E (sleepwalking outside of the bedroom).** Patients with non-rapid eye movement (non-REM) parasomnia can sleepwalk away from the bed or even out of the bedroom, while those with REM sleep behavior disorder may sit up or jump out of bed but do not walk out of the bedroom. The other listed choices are more typical of REM sleep behavior disorder. For more information, refer to **page 1094** of the *Continuum* article "REM Sleep Behavior Disorder and Other REM Parasomnias."

14 The preferred response is **D (rapid eye movement [REM] sleep without atonia).** The core polysomnographic feature of REM sleep behavior disorder is REM sleep without atonia. This is based on tonic or phasic chin or limb muscle activity by EMG recording in multiple epochs of REM sleep. For more information, refer to **page 1095** of the *Continuum* article "REM Sleep Behavior Disorder and Other REM Parasomnias."

15 The preferred response is **D (sublateral dorsal nucleus).** During rapid eye movement (REM) sleep, glutamatergic neurons in the sublateral dorsal nucleus project to the nucleus raphe magnus and other nuclei of the ventromedial medulla. These neurons mediate motor atonia through inhibitory projections to spinal motor neurons. For more information, refer to **page 1098** of the *Continuum* article "REM Sleep Behavior Disorder and Other REM Parasomnias."

16 The preferred response is **E (venlafaxine).** Medications most likely to induce or worsen rapid eye movement (REM) sleep behavior disorder include serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants. For more information, refer to **page 1101** of the *Continuum* article "REM Sleep Behavior Disorder and Other REM Parasomnias."

17 The preferred response is **E (prazosin).** Prazosin at night is the recommended first-line pharmacologic treatment for nightmare disorder and posttraumatic stress disorder–associated nightmares. Prazosin is an α_1-adrenergic receptor antagonist and one of its common side effects is orthostatic hypotension. For more information, refer to **page 1111** of the *Continuum* article "REM Sleep Behavior Disorder and Other REM Parasomnias."

ARTICLE 6: NON–REM SLEEP PARASOMNIAS

18 The preferred response is **D (sleep terror).** This patient's sleep events consist of screaming and autonomic manifestations of fear for which he has partial memory. One episode was associated with jumping out of bed, which raises the possibility of rapid eye movement (REM) sleep behavior disorder, but the lack of explicit dream recall makes sleep terror more likely. For more information, refer to **page 1119** of the *Continuum* article "Non–REM Sleep Parasomnias."

19 The preferred response is **B (provide safety counseling).** This patient should receive safety counseling regarding the risks of physical injury during sleepwalking and avoiding sleep deprivation. Since it was a single provoked event after years of no events, pharmacotherapy is not indicated at this time. Polysomnography is generally not indicated for non-rapid eye movement (non-REM) parasomnias. For more information, refer to **page 1125** of the *Continuum* article "Non-REM Sleep Parasomnias."

20 The preferred response is **C (regionally increased delta activity).** The behavioral episodes of non-rapid eye movement (non-REM) parasomnias are associated with increased delta activity, which is typically regional and is the hallmark of stage N3 sleep, indicating the incomplete electrical transition from sleep to wake. For more information, refer to **page 1124** of the *Continuum* article "Non-REM Sleep Parasomnias."

21 The preferred response is **E (zolpidem).** Several prescription insomnia medications can increase the likelihood of non-rapid eye movement (non-REM) parasomnias. Clonazepam, gabapentin, and melatonin may be effective treatments. For more information, refer to **page 1123** of the *Continuum* article "Non-REM Sleep Parasomnias."

ARTICLE 7: RESTLESS LEGS SYNDROME AND OTHER COMMON SLEEP-RELATED MOVEMENT DISORDERS

22 The preferred response is **C (pramipexole).** Augmentation refers to a worsening of symptoms in response to medication used to treat restless legs syndrome. This is associated with dopaminergic medications and often occurs after an increase in dosage. Augmentation is more frequent with carbidopa/levodopa than with dopamine agonists. For more information, refer to **page 1133** of the *Continuum* article "Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders."

23 The preferred response is **B (diphenhydramine).** Medications that can aggravate or even cause restless legs syndrome include antihistamines such as diphenhydramine, antidepressant medications except for bupropion, antinausea drugs, and antipsychotic medications. For more information, refer to **page 1131** of the *Continuum* article "Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders."

24 The preferred response is **C (ferritin).** Restless legs syndrome is associated with iron deficiency. Serum ferritin should be obtained in the morning after fasting. Transferrin saturation percentage should also be checked. Iron supplementation is indicated if the serum ferritin is less than 75 ng/mL or if transferrin saturation is less than 20% to 25%. Ferritin can be falsely high in some situations so a low transferrin saturation even with normal serum ferritin should prompt a trial of iron supplementation. For more information, refer to **page 1132** of the *Continuum* article "Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders."

25 The preferred response is **E (rotigotine).** Treatment with dopamine agonists such as rotigotine may be associated with impulse control disorders such as excessive spending or gambling. For more information, refer to **page 1133** of the *Continuum* article "Restless Legs Syndrome and Other Common Sleep-Related Movement Disorders."

ARTICLE 8: CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

26 The preferred response is **D (scheduled melatonin).** Blind individuals with non-24-hour sleep-wake rhythm disorder may benefit from scheduled melatonin. Timed light exposure may be beneficial for sighted individuals with this disorder but would not be expected to help completely blind individuals who have no light perception. For more information, refer to **page 1155** of the *Continuum* article "Circadian Rhythm Sleep-Wake Disorders."

27 The preferred response is **E (suprachiasmatic nucleus).** The hypothalamic suprachiasmatic nucleus is the master clock in mammals, receiving light input from retinal ganglion cells and regulating the timing of rhythmic behaviors. For more information, refer to **page 1149** of the *Continuum* article "Circadian Rhythm Sleep-Wake Disorders."

28 The preferred response is **A (blue).** The shorter wavelengths of visible light (ie, blue light) are known to be the most powerful photic stimulus suppressing melatonin. For more information, refer to **page 1149** of the *Continuum* article "Circadian Rhythm Sleep-Wake Disorders."

29 The preferred response is **B (permanent Standard Time).** Year-round observation of Standard Time would best align environmental cues with the internal clock. Shifting of the clock forward 1 hour in the spring and back 1 hour in the fall (Daylight Saving Time) disrupts the circadian rhythm by misaligning the timing of morning light with clock time. Making Daylight Saving Time permanent would further increase circadian disruption. For more information, refer to **page 1159** of the *Continuum* article "Circadian Rhythm Sleep-Wake Disorders."

ARTICLE 9: INSOMNIA

30 The preferred response is **B (history alone).** The diagnosis of insomnia disorders is based on a history of difficulty sleeping despite adequate opportunity and the presence of associated daytime dysfunction. The diagnosis can be made by history alone and objective verification of subjective symptoms is not required. For more information, refer to **page 1166** of the *Continuum* article "Insomnia."

31 The preferred response is **A (γ-aminobutyric acid [GABA]).** GABA is the primary inhibitory neurotransmitter of the central nervous system. Most US Food and Drug Administration (FDA)-approved medications for the treatment of insomnia work via modulation of the GABA system including benzodiazepines and benzodiazepine receptor agonists. For more information, refer to **page 1175** of the *Continuum* article "Insomnia."

32 The preferred response is **D (suvorexant).** Orexin (hypocretin) neuropeptides A and B cause arousal and wakefulness via the upregulation of multiple transmitter pathways. Dual orexin receptor antagonists induce sleep by blocking the orexin (hypocretin) system. There are three dual orexin receptor antagonist medications available now: suvorexant, lemborexant, and daridorexant. For more information, refer to **page 1177** of the *Continuum* article "Insomnia."

33 The preferred response is **C (mirtazapine).** Histamine is a neurotransmitter that induces wakefulness. The antagonism of histamine receptors is effective in the induction and maintenance of sleep. Most sedating antidepressants work through histamine antagonism. Low doses of mirtazapine are highly selective for histamine receptors. For more information, refer to **page 1179** of the *Continuum* article "Insomnia."

ARTICLE 10: SLEEP DISORDERS IN PATIENTS WITH NEUROLOGIC DISEASE

34 The preferred response is **B (obstructive sleep apnea).** Obstructive sleep apnea is an independent risk factor for stroke and is also linked with individual stroke risk factors. It is highly prevalent among patients with atrial fibrillation and is arrhythmogenic, associated with both sympathetic activation and atrial electrophysiological changes. For more information, refer to **page 1188** of the *Continuum* article "Sleep Disorders in Patients with Neurologic Disease."

35 The preferred response is **D (neuromyelitis optica spectrum disorder [NMOSD]).** One of the six core clinical features of NMOSD is symptomatic narcolepsy or acute diencephalic clinical syndrome with typical diencephalic MRI lesions. Similarly, narcolepsy may occur in multiple sclerosis when plaques occur in the hypothalamic area and secondary damage occurs to the orexin (hypocretin) neurons. For more information, refer to **page 1196** of the *Continuum* article "Sleep Disorders in Patients with Neurologic Disease."

36 The preferred response is **B (caffeine).** This older patient with headaches that occur exclusively during sleep at the same time every night and last more than 15 minutes after awakening meets the criteria for the primary headache disorder hypnic headache. Caffeine is first-line abortive therapy for this headache type. For more information, refer to **page 1198** of the *Continuum* article "Sleep Disorders in Patients with Neurologic Disease."

ARTICLE 11: SLEEP DISORDERS IN CHILDHOOD

37 The preferred response is **D (midface hypoplasia).** The nightly pressure of the mask on the growing facial structures of pediatric patients with obstructive sleep apnea treated with positive airway pressure therapy may result in midface hypoplasia. This complication may be mitigated by regular mask fittings but may require interventions for correction including rapid maxillary expansion and myofunctional therapy. For more information, refer to **page 1211** of the *Continuum* article "Sleep Disorders in Childhood."

38 The preferred response is **D (precocious puberty).** Narcolepsy type 1 is often associated with endocrine and metabolic changes at disease onset. Precocious puberty is a frequent concomitant condition to pediatric narcolepsy, occurring in approximately 17% of patients. In addition, rapid weight gain with resultant obesity often occurs at the time of onset of pediatric narcolepsy. For more information, refer to **page 1223** of the *Continuum* article "Sleep Disorders in Childhood."

ARTICLE 12: SLEEP DEPRIVATION AND ITS CONSEQUENCES

39 The preferred response is **C (major depression).** Sleep deprivation is linked to many psychiatric disorders, including anxiety, hallucinations, delirium, psychosis, and as a trigger for mania episodes in bipolar disorder. But acute sleep deprivation may cause short-term remission of major depressive disorder in about half of patients. For more information, refer to **page 1238** of the *Continuum* article "Sleep Deprivation and Its Consequences."

40 The preferred response is **C (impairment of endothelium-dependent vasodilation)**. Chronic sleep deprivation may increase the risk of cardiovascular disease through its activation of the sympathetic nervous system, increasing heart rate, blood pressure, and catecholamine activity and impairing the physiologic nocturnal dip in blood pressure during non-rapid eye movement (non-REM) sleep. It is also associated with dysfunctional nitric oxide–mediated endothelium-dependent vasodilation, activation of immune responses affecting cholesterol mechanisms, and results in persistently elevated levels of immunosuppressive hormones. For more information, refer to **page 1241** of the *Continuum* article "Sleep Deprivation and Its Consequences."

LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue, participants will be able to:

- Identify and describe basic concepts related to brain structures involved in the regulation of wakefulness and sleep physiology, and their interactions with pharmacologic interventions and circadian rhythms
- Evaluate patients with sleep-related symptoms, the association between neurologic conditions and sleep disorders, and testing modalities to diagnose and monitor common sleep disorders
- Identify common presentations of narcolepsy and idiopathic hypersomnia and apply evidence-based clinical guidelines for the treatment of patients with central disorders of hypersomnolence
- Describe the epidemiology, pathophysiology, clinical presentation, and diagnosis and treatment options for obstructive sleep apnea
- Describe parasomnias that arise from rapid eye movement (REM) sleep, including REM sleep behavior disorder and its diagnosis, management, and association with neurodegenerative diseases
- Recognize the clinical characteristics, classification, and treatments of parasomnias that occur in non-REM sleep
- Discuss the evaluation and management of restless legs syndrome and other sleep-related movement disorders
- Describe the ubiquity of physiologic clocks in biological functions and the impact of circadian rhythm sleep-wake disorders on neurologic conditions and overall health, and convey the importance of a healthy circadian rhythm to patients and advise them on management strategies
- Describe the diagnosis and management of insomnia, including the role of pharmacologic and nonpharmacologic therapies and the growing use of technology within this field
- Elucidate the growing body of evidence showing a bidirectional relationship between sleep and multiple neurologic disease states
- Describe the pathophysiology, clinical presentation, diagnosis, and management of common pediatric sleep disorders
- Identify, define, and describe the signs and symptoms of sleep deprivation and its main consequences, and apply this knowledge to neurologic practice

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue covers the following core competencies:

- Patient Care and Procedural Skills
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

LIST OF ABBREVIATIONS

Sleep Neurology

3-P	Three-process
AAN	American Academy of Neurology
ADHD	Attention deficit hyperactivity disorder
AHI	Apnea-hypopnea index
ALS	Amyotrophic lateral sclerosis
APAP	Autoadjusting positive airway pressure
APOE	Apolipoprotein E gene
BASIC	Brain Attack Surveillance in Corpus Christi
BEARS	Bedtime problems, excessive daytime sleepiness, awakenings during the night, regularity and duration of sleep, and sleep-disordered breathing
BiPAP	Bilevel positive airway pressure
BMAL1	Basic helix-loop-helix ARNT-like 1
BMI	Body mass index
CA	Control-adjusted
CAI	Central apnea index
CBT-I	Cognitive behavioral therapy for insomnia
CK1 ε/δ	Casein kinase 1 ε/δ
CLOCK	Clock circadian regulator
CPAP	Continuous positive airway pressure
CRY1	Cryptochrome circadian regulator 1
CRY2	Cryptochrome circadian regulator 2
CSF	Cerebrospinal fluid
CT	Computerized tomography
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DST	Daylight Saving Time
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyography
ER	Extended release
FDA	US Food and Drug Administration
FDG-PET	Fludeoxyglucose positron emission tomography
GABA	γ-aminobutyric acid
GABA-ergic	γ-aminobutyric acid–mediated
H1N1	Influenza A
HLA	Human leukocyte antigen
ICSD-3-TR	*International Classification of Sleep Disorders, Third Edition, Text Revision*
ICU	Intensive care unit
IL	Interleukin
IV	Intravenous
KLS	Kleine-Levin syndrome
MAOI	Monoamine oxidase inhibitor
MESA	Multi-Ethnic Study of Atherosclerosis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSLT	Multiple sleep latency test
NIHSS	National Institutes of Health Stroke Scale
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PER1	Period circadian regulator 1
PER2	Period circadian regulator 2
PER3	Period circadian regulator 3
PSG	Polysomnogram
PTSD	Posttraumatic stress disorder
RBD	Rapid eye movement sleep behavior disorder
REM	Rapid eye movement
RLS	Restless legs syndrome
RNA	Ribonucleic acid
RWA	Rapid eye movement sleep without atonia
SAT	Scholastic Aptitude Test
SAVE	Sleep Apnea Cardiovascular Endpoints
SINBAR	Sleep Innsbruck Barcelona
Sleep SMART	Sleep for Stroke Management and Recovery Trial
SNRI	Serotonin-norepinephrine reuptake inhibitor
SPECT	Single-photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
ST	Standard Time
TBI	Traumatic brain injury
TNF-α	Tumor necrosis factor-α
TRACK-TBI	Transforming Research and Clinical Knowledge in Traumatic Brain Injury
VLPO	Ventrolateral preoptic

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LIFELONG LEARNING IN NEUROLOGY®

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SLEEP NEUROLOGY

ARTICLE 1: CLINICAL NEUROBIOLOGY OF SLEEP AND WAKEFULNESS

Pablo R. Castillo, MD, FAAN. Continuum (Minneap Minn). August 2023;
29 (4 Sleep Neurology):1016–1030.

ABSTRACT

OBJECTIVE:

This article focuses on novel neuronal mechanisms of sleep and wakefulness and relates basic science developments with potential translational implications in circadian neurobiology, pharmacology, behavioral factors, and the recently integrated potential pathways of sleep-related motor inhibition.

LATEST DEVELOPMENTS:

During the past decade, remarkable advances in the molecular biology of sleep and wakefulness have taken place, opening a promising path for the understanding of clinical sleep disorders. Newly gained insights include the role of astrocytes in sleep brain homeostasis through the glymphatic system, the promotion of memory consolidation during states of reduced cholinergic activity during slow wave sleep, and the differential functions of melatonin receptors involving regulation of both circadian rhythm and sleep initiation. Ongoing investigations exploring sleep and circadian rhythm disruptions are beginning to unlock pathophysiologic aspects of neurologic, psychiatric, and medical disorders.

ESSENTIAL POINTS:

An understanding of sleep and circadian neurobiology provides coherent and biologically credible approaches to treatments, including the identification of potential targets for neuromodulation.

KEY POINTS

- Caffeine promotes wakefulness primarily through antagonism of adenosine receptors.
- During slow-wave sleep, thalamocortical networks become relatively unresponsive, potentially preventing interference from external sensory inputs. Disorders of arousal such as sleepwalking and sleep terrors emerge from slow-wave sleep.
- The sublaterodorsal tegmental nucleus and ventromedial medulla constitute the rapid eye movement (REM) sleep atonia circuit; lesions in this area prevent physiologic REM sleep paralysis, which results in REM sleep without atonia.

- REM sleep without atonia can be triggered in various disease states (such as synucleinopathies) or exacerbated by different drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), mirtazapine, venlafaxine, and beta-blockers.
- A portion of orexin (hypocretin) neurons inhibit REM sleep by sending input to REM-off (REM-suppressing) neurons in the locus coeruleus, ventrolateral periaqueductal gray, and dorsal raphe nuclei, while other orexin (hypocretin) neurons exhibit REM sleep–related activation.
- The basolateral amygdala contributes to the slow-wave sleep–to–REM sleep transition and also sends extensive γ-aminobutyric acid–mediated (GABA-ergic) projections to brainstem regions that promote waking muscle tone and may trigger cataplexy in response to emotions in patients with narcolepsy.
- Claustrum neurons project over large cortical regions, which allows them to influence sleep slow oscillations.
- The habenula receives information from the melanopsin-containing intrinsically photosensitive retinal ganglion cells, potentially representing an extended circadian system.
- Circadian rhythm disruption is associated with a greater risk of metabolic dysregulation and may also have pathophysiologic effects on psychiatric and neurodegenerative disorders.
- Coordinating activity between parahippocampal ripples and widespread sleep spindles supports the concept of a hippocampal-neocortex coupling and information transfer during sleep.
- The orexin (hypocretin) system is involved in both the promotion of wakefulness and the regulation of feeding, motivation, endocrine, and autonomic activities. Narcolepsy type 1 is a consequence of orexin (hypocretin) system dysfunction.
- Although caffeine promotes alertness, the subjective alerting benefit may be at the expense of a reduction of slow-wave sleep duration.

ARTICLE 2: CLINICAL EVALUATION OF THE SLEEPY AND SLEEPLESS PATIENT

Samuel A. Taylor Jr, MD, MS. Continuum (Minneap Minn). August 2023;
29 (4 Sleep Neurology):1031-1044.

ABSTRACT

OBJECTIVE:

This article addresses the approach to the evaluation of patients who present to a neurologist with excessive daytime sleepiness or difficulty sleeping.

LATEST DEVELOPMENTS:

Greater emphasis on the importance of sleep reflects the growing scientific understanding that sleep is critical to overall health and well-being. Consumer sleep technologies, which measure parameters related to sleep, may provide insight into an individual's sleep-related symptoms and tendencies and have a role in patient-centered sleep evaluation when used within an appropriate clinical context.

ESSENTIAL POINTS:

A thorough review of a patient's history and physical examination findings are important components of the assessment and management of their sleep-related symptoms. An understanding of how the clinical context relates to the categorization of sleep disorders can impact a patient's symptoms, comorbid neurologic disorders, and overall well-being. Many neurologic conditions are strongly associated with sleep disturbance, risk factors for the development of a sleep disorder, or both. Therefore, it is critical for neurologists to be familiar

and comfortable with taking a focused sleep history. Modalities such as in-laboratory polysomnography, home sleep apnea testing, multiple sleep latency testing, and actigraphy, as well as contextualized and prudent use of data obtained from consumer sleep technologies, can be helpful in appropriately selected patients. Mindful integration of these objective data facilitates the diagnosis and management of sleep disorders.

KEY POINTS

- Familiarity with the main categories of sleep-wake disorders provides a framework for differential diagnosis to guide diagnostic and therapeutic care plans.
- The evaluation of excessive daytime sleepiness requires direct inquiry about the presence of associated sleep paralysis, sleep-related hallucinations, cataplexy, and disrupted or fragmented sleep.
- Understanding the 3-P model of insomnia (predisposing, precipitating, and perpetuating factors) is important to both contextualize the patient's sleeplessness and provide a solid foundation for patient education regarding the assessment and care plan.
- The four manifestations of insomnia include difficulty initiating sleep, difficulty maintaining sleep, unintended early morning awakenings, and overall poor sleep quality despite adequate time allowed to sleep.
- Individuals with neurodegenerative disorders such as Parkinson disease and dementia with Lewy bodies more commonly experience recalcitrant or progressive insomnia.
- Non–rapid eye movement (non-REM) parasomnias of childhood, intrinsic circadian rhythm sleep-wake disorders, narcolepsy, and restless legs syndrome can have hereditary components.
- The Mallampati system, developed to assess the complexity of intubation and airway management during sedation or anesthesia, describes various levels of oral airway patency and is used stratify the risk of sleep-disordered breathing
- The Epworth Sleepiness Scale is useful for following sleepiness (and treatment response) in the same individual over time, but it is not used to compare levels of sleepiness between individuals.
- The in-laboratory, fully attended polysomnogram is the gold standard test for the evaluation of sleep and identification of most sleep disorders.
- Diagnostic testing with polysomnography or home sleep apnea testing is not recommended for the diagnosis or management of insomnia.
- The multiple sleep latency test is the current gold standard for quantifying sleepiness and is used in the diagnosis of central disorders of hypersomnolence such as narcolepsy and idiopathic hypersomnia.
- A multiple sleep latency test showing a mean sleep latency of less than 8 minutes with two or more sleep-onset REM periods is supportive of a diagnosis of narcolepsy if all other causes of hypersomnolence have been excluded.
- Medications that might affect wakefulness or confound multiple sleep latency test results are typically avoided for approximately 2 weeks or 5 pharmacological half-lives of the medication to minimize their effects on testing.
- In the proper clinical context, actigraphy can be a useful tool to increase measurement objectivity in the evaluation of insomnia and circadian rhythm sleep-wake disorders.
- Home sleep apnea tests are limited cardiorespiratory tests used for the diagnosis of obstructive sleep apnea. These devices are not used to diagnose other sleep disorders.
- Consumer sleep technologies may have a role in the clinical evaluation and management of sleep disorders and the optimization of sleep quality, but they are currently not sufficient to establish a diagnosis of any sleep disorder.
- If drowsiness develops while driving, the recommended actions include pulling over as soon as is safely possible and napping for 15 to 20 minutes, using caffeine, or allowing someone else who is alert to drive.

ARTICLE 3: CENTRAL DISORDERS OF HYPERSOMNOLENCE

Margaret Blattner, MD, PhD; Kiran Maski, MD, MPH. Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1045–1070.

ABSTRACT

OBJECTIVE:

The goals of this article are to describe the clinical approach to and management of patients with central disorders of hypersomnolence, and to understand and differentiate available diagnostic tools.

LATEST DEVELOPMENTS:

Updated clinical practice guidelines for the treatment of central disorders of hypersomnolence and narcolepsy specifically highlight new treatment options. Approval for a lower-sodium oxybate formulation that contains 92% less sodium than the standard sodium oxybate for the treatment of narcolepsy and idiopathic hypersomnia adds to the number of medications available for these disorders, allowing for a more tailored management of symptoms.

ESSENTIAL POINTS:

Central disorders of hypersomnolence are characterized by excessive daytime sleepiness that impacts daily functions. These disorders can be differentiated by obtaining a detailed clinical sleep history and by a thoughtful interpretation of sleep diagnostic testing. Tailoring treatment approaches to meet the needs of individuals and accounting for medical and psychiatric comorbidities may improve quality of life.

KEY POINTS

- In the *International Classification of Sleep Disorders, Third Edition, Text Revision*, central disorders of hypersomnolence include narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia associated with a psychiatric disorder, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, and insufficient sleep syndrome.
- The Epworth Sleepiness Scale can be quickly administered and is commonly used to identify sleepiness and assess the severity of daytime sleepiness.
- Disorders of hypersomnolence are typically evaluated by overnight polysomnography followed by the multiple sleep latency test.
- Optimally, medications that impact sleep propensity and sleep architecture should be tapered and discontinued at least 2 weeks prior to the multiple sleep latency test.
- Many patients with narcolepsy have symptoms of rapid eye movement (REM) sleep intruding into their waking state, including cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis.
- Cataplexy is a generalized or partial loss of muscle tone, typically triggered by strong positive emotions, including laughter or anticipation.
- The narcolepsy tetrad of sleepiness, cataplexy, sleep paralysis, and sleep-related hallucinations is present in only about 45% of people with narcolepsy type 1.
- People with narcolepsy have disrupted nocturnal sleep, with increased arousal index, sleep stage transitions, and time spent awake after sleep onset relative to healthy sleepers.
- Patients with narcolepsy are at increased risk of developing medical and psychiatric comorbidities, including obesity and hypertension; depression has been reported in more than one-third of patients with narcolepsy.

- Narcolepsy type 1 is likely caused by immune-mediated selective loss of orexin (hypocretin)-producing neurons in the hypothalamus.
- The multiple sleep latency test has high diagnostic validity and reliability in narcolepsy; however, the reliability is poor in narcolepsy type 2 and idiopathic hypersomnia.
- Cataplexy can be seen in the pediatric genetic syndromes Niemann-Pick disease type C, Angelman syndrome, Norrie disease, Prader-Willi syndrome, DNMT1-complex disorder, and myotonic dystrophy.
- Idiopathic hypersomnia is clinically characterized by excessive daytime sleepiness, severe difficulty waking from sleep (sleep inertia), and daytime brain fog or cognitive cloudiness.
- Patients with idiopathic hypersomnia can have prolonged sleep duration with more than 10 to 11 hours of nocturnal sleep in addition to long daytime naps.
- The physiology underlying the symptoms of idiopathic hypersomnia is not well understood and could reflect modified γ-aminobutyric acid (GABA) responsiveness, dysautonomia, or circadian rhythm dysfunction.
- Patients diagnosed with either narcolepsy type 2 or idiopathic hypersomnia may present with similar clinical phenotypes, and current diagnostic differentiation is based on the presence of sleep-onset REM periods during the multiple sleep latency test.
- Scheduled daytime naps of 15 to 30 minutes can partially ameliorate drowsiness and improve alertness for patients with narcolepsy; naps are typically less helpful for sleepiness related to idiopathic hypersomnia.
- Oxybates (sodium oxybate and lower-sodium oxybate) reduce sleepiness, disrupted nocturnal sleep, and cataplexy in patients with narcolepsy.
- Following postacute COVID-19 infection, more than half of patients with persistent symptoms describe fatigue and about a quarter of patients with persistent symptoms describe sleep difficulties.
- Clinical features of Kleine-Levin syndrome include episodic sleepiness and mood and behavioral changes (hyperphagia, irritability, hypersexuality, and cognitive changes).
- Most commonly, mood changes during episodes of Kleine-Levin syndrome include apathy and derealization. Hyperphagia and hypersexuality each occur in approximately 50% of patients.
- Lithium may decrease the frequency, severity, and duration of episodes in Kleine-Levin syndrome.

ARTICLE 4: OBSTRUCTIVE SLEEP APNEA

Karin G. Johnson, MD, FAAN, FAASM. Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1071–1091.

ABSTRACT

OBJECTIVE:

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing. This article describes advances in the diagnosis, testing, treatment, and monitoring of OSA.

LATEST DEVELOPMENTS:

Home sleep apnea testing and in-laboratory polysomnography are the most commonly used diagnostic tools in the identification and monitoring of OSA, but new methods for diagnosis and at-home monitoring of treatment response are being developed and validated. While the apnea-hypopnea index is regularly used to define OSA severity, recognition is increasing of its inability to risk-stratify patients. Other sleep study data including arousal threshold, hypoxic burden, and pulse rate variability as well as clinical characteristics can help with risk stratification. The most effective treatment is continuous positive airway pressure (CPAP), which can be limited by adherence and tolerance in some patients. Newer masks and comfort features including heated tubing and expiratory pressure relief may improve tolerance to positive airway pressure (PAP) therapy. Additional treatment options include other PAP modalities, mandibular

advancement devices, tongue stimulation therapy, negative inspiratory pressure, nasal expiratory pressure valves, nasal congestion treatments, upper airway surgeries including hypoglossal nerve stimulation, and medications.

ESSENTIAL POINTS:

OSA is a common disorder that causes sleep and daytime symptoms and increases the risk of neurologic and medical complications. Neurologists should be aware of atypical presentations and understand the diagnostic and treatment options.

KEY POINTS

- Obstructive sleep apnea (OSA) is the most common subtype of sleep-disordered breathing.
- OSA results from repetitive narrowing or collapse of the upper airway that leads to arousals or intermittent hypoxia.
- The severity of OSA is typically determined by the number of events per hour, or the apnea-hypopnea index or respiratory event index.
- The apnea-hypopnea index does not accurately predict treatment response, cardiovascular risk, or death so hypoxic burden, heart rate variability, and flow limitation may help inform risks.
- Women are more likely to present with atypical OSA symptoms including sleep maintenance insomnia and fatigue.
- Obesity is commonly associated with OSA, but about 30% of patients with OSA are not obese.
- Sleeping in a supine position, drinking alcohol, and smoking tobacco can worsen OSA.
- Untreated OSA has been associated with increased prevalence, worsened symptom control, or both in many neurologic disorders.
- Home sleep apnea testing can underestimate the severity of OSA, so in-laboratory polysomnography is recommended if home sleep apnea testing results are normal.
- Polysomnography rather than home sleep apnea testing is recommended for patients with a high risk of central sleep apnea, obesity hypoventilation, comorbid lung disease including chronic obstructive pulmonary disease, comorbid neuromuscular disorders, evaluation of nonrespiratory sleep disorders including parasomnias, and sleep-related breathing disorders in children.
- Photoplethysmography can detect changes in blood volume allowing for arterial pulse wave analysis and peripheral arterial tone, which can provide information about autonomic nervous system response, sleep stage, and arousals.
- Direct-to-consumer sleep and oxygen monitoring devices may increase patient awareness and engagement regarding sleep health.
- All patients with OSA should be counseled on conservative measures, including nonsupine sleeping positions, nasal congestion therapy, smoking and alcohol cessation, and weight loss.
- Continuous positive airway pressure (CPAP) therapy acts as a pneumatic splint and prevents collapse of the upper airway.
- Auto-adjusting positive airway pressure devices increase the delivered pressure in response to obstructive features such as apneas, hypopneas, snoring, or flow limitation and reduce the delivered pressure in response to normal breathing.
- High mask leak can lead to inadequate treatment response either to direct disruptions from the leak itself arousing the patient or from subtherapeutic pressure delivery.
- Bilevel positive airway pressure, adaptive servoventilation, and volume-assured pressure support may be needed for comfort, to stabilize breathing, or to ensure a stable level of ventilation.
- Adherence data, which can often be followed remotely, can assist with troubleshooting intolerance and identifying suboptimal treatment response.
- Tonsillectomy and adenoidectomy are generally the most effective OSA treatments in children.
- Alternative treatments for OSA include weight loss, positional therapy, mandibular advancement devices, nasal congestion treatments, and unilateral hypoglossal nerve stimulation and other airway surgeries.

- Pharmacotherapies including carbonic anhydrase inhibitors, reboxetine, and hyoscine butylbromide may decrease some patients' apnea-hypopnea index scores.

ARTICLE 5: REM SLEEP BEHAVIOR DISORDER AND OTHER REM PARASOMNIAS

Roneil Malkani, MD, MS. Continuum (Minneap Minn). August 2023;
29 (4 Sleep Neurology):1092–1116.

ABSTRACT

OBJECTIVE:

This article reviews rapid eye movement (REM) sleep behavior disorder (RBD) and other REM sleep parasomnias, particularly recurrent isolated sleep paralysis and nightmare disorder.

LATEST DEVELOPMENTS:

People with RBD have dream enactment behaviors that can be distressing and cause injuries to themselves or a bed partner. Diagnosis of RBD still requires video polysomnography but new evaluative techniques are emerging. Automatic scoring of REM sleep without atonia, the polysomnographic RBD feature, has led to clearer diagnostic cutoff values. Isolated RBD is strongly linked with neurodegenerative disorders, particularly α-synucleinopathies, with a median latency to neurodegenerative disease diagnosis of 8 years. Mounting imaging, electrophysiologic, and pathologic evidence supports neurodegenerative changes in patients with isolated RBD. Safety precautions should be reviewed with patients to reduce the risk of injury. Clonazepam and melatonin are first-line agents for RBD symptoms, and rivastigmine appears to be beneficial for RBD in people with mild cognitive impairment. For nightmare disorder, image rehearsal therapy is effective and can be delivered through online platforms.

ESSENTIAL POINTS:

While RBD symptoms can often be managed, patients with isolated RBD should be monitored for signs and symptoms of impending neurodegenerative disease. Individuals who wish to know about the associated risk should be counseled accordingly to allow planning and involvement in research if they choose. Exercise may have some neuroprotective effects, although no treatment has been shown to modify the neurodegenerative risk.

KEY POINTS

- Diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) requires historical or video polysomnographic evidence of dream enactment behaviors and REM sleep without atonia.
- Dream enactment behaviors in RBD can include punching, kicking, or falling from the bed, which can cause injuries to the patient and bed partner.
- Dream enactment in RBD can happen across the night but tends to occur in the last half of the sleep period, which is usually richer in REM sleep.
- Polysomnography is important to evaluate for RBD mimics, such as sleep apnea or periodic limb movements of sleep.
- Questionnaires can aid in RBD screening but have high false-positive rates compared to polysomnography-confirmed RBD diagnosis.

- RBD is more common in men among people 50 years old or older but can affect men and women equally in those younger than 50 years old.
- Antidepressant medications may induce RBD via disrupted inhibition of REM-on neurons (which control motor atonia in the nondisease state).
- RBD can start after the onset of neurodegenerative disease or can be comorbid with other disorders, such as narcolepsy.
- In people with known neurodegenerative disease, the presence of RBD predicts worse motor and cognitive function.
- Events seen in RBD secondary to narcolepsy are more evenly distributed throughout the sleep period compared with the events noted in the setting of isolated RBD, which are more frequent in the second half of the sleep period.
- The most common causes of drug-induced RBD are antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Symptoms can take several months to resolve after drug discontinuation.
- People with isolated RBD have a high lifetime risk of neurodegenerative disease, particularly α-synucleinopathies; about one-half of those with RBD will develop a neurodegenerative disease over 8 years of follow-up after RBD diagnosis.
- Factors that predict an increased risk of phenoconversion in isolated RBD include abnormal dopamine transporter and substantia nigra imaging, pathologic markers, and autonomic, motor, and cognitive dysfunction.
- Reviewing safety precautions with patients (eg, pad or remove nearby furniture, remove potentially injurious objects, add a bedrail to reduce risk of injury) is critical to reducing the risk of injury from dream enactment behavior.
- Clonazepam and melatonin are the first-line agents to suppress dream enactment behaviors. Treatment choice requires consideration of the RBD subtype and comorbidities, such as dementia.
- Patients should be offered information on the potential health risks of RBD, and if desired more specific information on the risk of neurodegeneration should be provided.
- Recurrent isolated sleep paralysis involves repeated episodes of sleep paralysis that cause distress and are not associated with another underlying disorder such as narcolepsy.
- Sleep paralysis can be triggered by sleep deprivation, jet lag, shift work, and supine sleep, and is more common in those with posttraumatic stress disorder.
- Management of recurrent isolated sleep paralysis may include reassurance, behavioral strategies, positional therapy, and tricyclic or other antidepressants.
- Nightmares are distressing, frightening dreams that involve threats to self or others. In nightmare disorder, one has recurrent nightmares that result in distress or functional impairment.
- Nightmares are common in people with posttraumatic stress disorder and tend to be related to the traumatic incident.
- Management of nightmare disorder includes cognitive behavioral therapy, particularly image rehearsal therapy, and medications such as prazosin.

ARTICLE 6: NON–REM SLEEP PARASOMNIAS

Andrew R. Spector, MD. Continuum (Minneap Minn). August 2023;
29 (4 Sleep Neurology):1117–1129.

ABSTRACT

OBJECTIVE:

Non–rapid eye movement (non-REM) parasomnias are common across the lifespan. This article describes the manifestations, diagnosis, and management of non-REM parasomnias in adults and discusses the social implications of these conditions.

LATEST DEVELOPMENTS:

Non-REM parasomnias represent a hybrid state of wakefulness and sleep, often triggered by events that increase the frequency of arousals or make it more difficult to fully arouse from sleep. Sleep deprivation, certain medications, and untreated obstructive sleep apnea are known to provoke parasomnias, particularly in those who are genetically predisposed. Non-REM parasomnias include disorders of arousal (ie, sleepwalking, sleep terrors, and confusional arousals), sleep-related eating disorder, and exploding head syndrome. Clinical overlap exists between sleep-related eating disorder and disorders of arousal, suggesting that sleep-related eating disorder may be a fourth disorder of arousal or a manifestation of sleepwalking. Exploding head syndrome is a unique parasomnia of uncertain etiology.

ESSENTIAL POINTS:

Non-REM parasomnias can range from minor nuisances to severe, life-altering events. While some patients with non-REM parasomnia experience significant consequences during sleep, wakefulness, or both, non-REM parasomnias do not pose a major risk to most patients. For all patients with non-REM parasomnias, safety should be explicitly discussed and addressed. Nonpharmacologic treatment should be prioritized, as increasing total sleep time, avoiding triggering substances, and treating comorbid sleep disorders is often sufficient for the management of non-REM parasomnias. If symptoms persist despite these interventions, treatment with clonazepam or other medications can be considered.

KEY POINTS

- Sleepwalking, sleep terrors, and confusional arousals are collectively known as disorders of arousal.
- Disorders of arousal are characterized by a mixed state of sleep and wakefulness with reduced awareness, responsiveness, and recall despite performing behaviors that would typically only occur when awake.
- People who sleepwalk can perform surprisingly complex tasks, often in a manner and with results that would not be expected if they had been fully awake.
- Sleep terrors are distinct from nightmares. Sleep terrors occur earlier in the night and are followed by limited recall, whereas nightmares tend to be later in the sleep period with good post-event recall.
- Sexsomnia is a rare but socially disturbing form of confusional arousal in which patients partially awaken and perform sexual acts without awareness or memory.
- Sleep-related eating disorder is characterized by high-volume, high-calorie, or unsafe eating in an altered state of consciousness during the night.
- Exploding head syndrome is characterized by the sudden sensation of a loud noise in the head during the transition from wake to sleep.

- Typically, non–rapid eye movement (REM) parasomnias occur earlier in the night than REM parasomnias and are less frequently associated with vivid dream imagery and dream recall.
- Nocturnal frontal lobe epilepsy can manifest as "agitated somnambulism," distinguished from primary sleepwalking with an EEG that captures the event and identifies epileptic discharges arising from stage N1 or N2 sleep rather than an arousal from stage N3.
- Non-REM parasomnias are frequently encountered in a familial pattern, which suggests that a genetic predisposition is likely.
- Non-REM parasomnias arise mostly from stage N3 sleep rather than stages N1 or N2, likely because the arousal threshold from stage N3 is greater and there is more potential for a partial or impaired arousal.
- Increased sleep pressure from sleep deprivation or medications can increase parasomnias by making it more difficult to awaken.
- Sleep fragmentation increases the risk of disordered arousals, which is the suspected mechanism behind the higher risk of non-REM parasomnias among patients with sleep-disordered breathing.
- Accurate diagnosis, patient safety, and improved quality of life are the primary goals of care for patients with non-REM parasomnias.
- Safety counseling and reassurance are the mainstay of treatment for non-REM parasomnias.
- Sleep deprivation should be avoided, as should sedative medications, particularly benzodiazepine receptor agonists (eg, zolpidem).
- While clonazepam is the traditional pharmacologic therapy for non-REM parasomnias, dopamine agonists, gabapentinoids, antidepressants, and melatonin have been found to be effective in some circumstances.
- Scant data exist about the frequency of non-REM parasomnias among different racial and ethnic groups in the United States.
- Sex differences are suspected in the specific cases of sleep-related eating disorder and sexsomnia, with the former being more prevalent in females and the latter being more prevalent in males.

ARTICLE 7: RESTLESS LEGS SYNDROME AND OTHER COMMON SLEEP-RELATED MOVEMENT DISORDERS

Meena Khan, MD, FAASM. Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1130–1148.

ABSTRACT

OBJECTIVE:

This article reviews common sleep-related movement disorders, including their clinical description, epidemiology, pathophysiology (if known), and evaluation and management strategies. This article will provide the reader with a good foundation for approaching concerns that are suggestive of sleep-related movement disorders to properly evaluate and manage these conditions.

LATEST DEVELOPMENTS:

α2δ Ligands, such as gabapentin enacarbil, can be used for the initial treatment of restless legs syndrome (RLS) or in those who cannot tolerate, or have developed augmentation to, dopamine agonists. Another option is the rotigotine patch, which has a 24-hour treatment window and may be beneficial for those who have developed augmentation with short-acting dopamine agonists. IV iron can improve RLS symptoms even in those whose serum ferritin level is between 75ng/mL

and 100ng/mL. At serum ferritin levels greater than 75ng/mL, oral iron will likely have minimal absorption or little effect on the improvement of RLS. Research has found an association between RLS and cardiovascular disease, particularly in people who have periodic limb movements of sleep.

ESSENTIAL POINTS:

RLS is the most common sleep-related movement disorder. Its pathophysiology is likely a combination of central iron deficiency, dopamine overproduction, and possibly cortical excitation. Treatment includes oral or IV iron. Dopaminergic medications can be very effective but often lead to augmentation, which limits their long-term use. Other sleep-related movement disorders to be aware of are sleep-related rhythmic movement disorder, nocturnal muscle cramps, sleep-related propriospinal myoclonus, sleep bruxism, and benign myoclonus of infancy.

KEY POINTS

- The prevalence of restless legs syndrome (RLS) in pregnancy is 2 to 3 times that of the general population and increases with each trimester, most often occurring in the third trimester and resolving after the first month following delivery.
- Tapering off or discontinuing antidepressants or dopamine receptor antagonists (eg, antipsychotic medications) should be discussed and considered in patients with RLS, if feasible.
- Evaluation for RLS should include checking serum ferritin levels and transferrin saturation. If serum ferritin is less than 75ng/mL or if transferrin saturation is less than 20% to 25%, iron therapy should be considered including IV iron if the patient cannot tolerate oral iron.
- Dopamine agonists and α2δ ligands are US Food and Drug Administration (FDA)-approved for the treatment of RLS. Patients on dopamine agonist therapy should be monitored for augmentation and impulse control symptoms.
- Opioids can be effective for RLS treatment and are typically used when other management strategies have failed.
- Lifestyle changes such as reducing or eliminating caffeine and alcohol can help with RLS symptom management.
- Periodic limb movements of sleep are repetitive movements of the lower extremities seen on a polysomnogram. They can be associated with other sleep disorders.
- Periodic limb movement disorder is defined by periodic limb movements of sleep on a polysomnogram that lead to daytime consequences in the absence of other sleep disorders.
- Periodic limb movements of sleep can be associated with sleep arousals, but associated arousals do not always occur, and most patients are not aware that they have limb movements during sleep.
- Periodic limb movement disorder treatments include dopamine agonists, gabapentin, and pregabalin.
- Sleep-related rhythmic movement disorder can be seen in children with and without autism spectrum disorder and other neuropsychiatric disorders.
- Sleep-related rhythmic movement disorder typically begins around age 9months and improves with age. Most cases resolve by age 10years.
- Secondary causes of nocturnal muscle cramps include medications, metabolic disorders, hypokalemia, hypocalcemia, hypomagnesemia, peripheral neuropathy, cardiovascular disease, cirrhosis, uremia, hypothyroidism, venous insufficiency, Parkinson disease, and multiple sclerosis.
- Magnesium supplementation may help in pregnant people with leg cramps.
- Sleep-related bruxism is a centrally mediated condition that can cause symptoms of jaw pain, tooth wear, and morning headaches. Disorders that cause arousals from sleep (eg, obstructive sleep apnea) can cause or exacerbate sleep-related bruxism.
- Risk factors that can contribute to sleep-related bruxism include tobacco and alcohol use, caffeine, stress,

anxiety, and disorders causing arousals from sleep such as obstructive sleep apnea, parasomnias, and gastroesophageal reflux disorder.

- Sleep-related bruxism can be treated with an oral appliance to decrease tooth damage and by addressing other conditions leading to arousals from sleep.
- Propriospinal myoclonus at sleep onset is characterized by brief truncal muscle jerks that result from signals generated within the thoracic spinal cord that propagate rostrally and caudally.
- Propriospinal myoclonus is typically idiopathic and occurs mainly in middle-aged men, although symptomatic propriospinal myoclonus (propriospinal myoclonus associated with a secondary cause) occurs more in women.
- When assessing for propriospinal myoclonus, imaging of the spinal cord may be appropriate even in the presence of a normal neurologic examination to evaluate for structural abnormalities.
- Benign sleep myoclonus of infancy occurs in neonates and infants and is defined as repetitive myoclonic jerks that occur during sleep and resolve with waking.
- Benign sleep myoclonus of infancy occurs during sleep only. It can start in the first month of life and resolves by age 1year in 97% of affected individuals. These infants are neurologically normal and do not have developmental abnormalities.
- Patients with benign sleep myoclonus of infancy that does not resolve by age 1year or has atypical features should be evaluated for epilepsy.

ARTICLE 8: CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Flavia B. Consens, MD. Continuum (Minneap Minn). August 2023;
29 (4 Sleep Neurology):1149-1166.

ABSTRACT

OBJECTIVE:

This article provides an overview of advances in the understanding of circadian rhythms and the health implications of circadian disruption.

LATEST DEVELOPMENTS:

Circadian medicine is a relatively new concept, with widespread overlap with many other areas of medicine. Circadian clocks rely on feedback loops that control the expression of many genes. Functional circadian oscillators exist at multiple physiologic levels and facilitate a multimodal clock mechanism. The suprachiasmatic nucleus is the central circadian pacemaker. Peripheral tissues can be entrained by other stimuli (such as food intake) and can uncouple from the suprachiasmatic nucleus pacemaker; this discovery may provide new therapeutic options for circadian rhythm disorders. Numerous modern developments have altered our circadian clocks and these changes are associated with poor health outcomes.

ESSENTIAL POINTS:

Circadian clocks are ubiquitous throughout our body and regulate multiple body functions. Several studies have highlighted that circadian disruption can result in significant negative mental and physical health consequences. A deeper understanding of the effects of misalignment between our circadian clocks and the external environment may ultimately have therapeutic implications for our health.

KEY POINTS

- Circadian rhythms are among the most basic mechanisms that help preserve health. Physiologic clocks regulate body temperature, hormone secretion, appetite, alertness, and most basic body functions.
- The suprachiasmatic nucleus is the master clock in mammals and coordinates secondary oscillators in other parts of the brain and body. Melatonin is regulated by the suprachiasmatic nucleus and can provide feedback and adjust the timing of suprachiasmatic nucleus activity.
- Genes that maintain autoregulatory feedback loops that regulate their own expression are part of the molecular circadian clock.
- Bright light in the evening causes a phase delay (shifts circadian clocks to a later time) and light in the early morning causes a phase advance (shifts circadian clocks to earlier times).
- The circadian alerting signal increases across the wake period, has a slight dip in the early to middle afternoon, and peaks in the early evening to maintain wakefulness until bedtime.
- Emerging studies suggest that multiple metabolic or nutritional cues (eg, time of food intake) are circadian-regulated components, which in turn can act as timing cues to regulate circadian physiology via reciprocal feedback mechanisms.
- Chronotype refers to an individual's preferred timing of sleep and wake; misalignment with the environment can cause "social jet lag." Later chronotypes have been associated with worse health outcomes.
- Circadian misalignment increases cardiovascular disease risk and is associated with an increased risk of cancer, autoimmune disease, and psychiatric disorders.
- Shift work disorder is seen when work occurs, at least in part, during the usual main sleep episode. Typically, total sleep is shortened by 1 to 4 hours and sleep quality is perceived as unsatisfactory during the available sleep time.
- Evidence shows that circadian disruption has a negative effect on neurologic disorders such as cerebrovascular disease, epilepsy, pain, migraine, multiple sclerosis, neurodegenerative disorders, and neurodevelopmental disorders.
- Delayed sleep-wake phase disorder occurs when sleep-wake times are delayed relative to conventional norms or desired times (ie, biological preference to go to bed late and wake up late) and is more common in adolescents and young adults.
- Irregular sleep-wake rhythm disorder is seen in people who lack clearly defined sleep-wake periods, with three discrete sleep episodes at variable times over 24 hours.
- People with non-24-hour sleep-wake rhythm disorder experience alternating symptoms of insomnia or daytime sleepiness due to misalignment of their endogenous period, which is usually slightly longer than 24 hours.
- In patients with circadian rhythm sleep-wake disorders, dim light exposure is prescribed for 2 hours before bedtime to facilitate endogenous melatonin release, and artificial bright light or sunlight exposure is prescribed for 60 minutes following wake-up time.
- Chronotherapy is the concept of timing therapy for neurologic and systemic disorders to optimize efficacy and minimize treatment side effects.
- Circadian rhythm sleep-wake disorders are clinical diagnoses that manifest due to misalignment between internal rhythms and the timing of external activities.
- Circadian disruption increases the risk for neurologic disorders across the lifespan.
- Light exposure before bedtime delays the internal clock, whereas light exposure in the morning advances circadian timing. Educational and behavioral counseling on good sleep hygiene, sleep scheduling, and light exposure are parts of circadian rhythm sleep-wake disorder treatment.
- Many chronic pain conditions are associated with disrupted circadian rhythm and sleep-wake rhythms, establishing a maladaptive feedback loop.
- Health disparities in circadian misalignment are common, with Black and Hispanic populations being twice as likely to work night shifts compared to White populations.

ARTICLE 9: INSOMNIA

Scott Kutscher, MD; Christine Juang, PhD, DBSM. Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1167–1187.

ABSTRACT

OBJECTIVE:

This article provides an overview of the current definitions, diagnostic tools, and overall management of insomnia.

LATEST DEVELOPMENTS:

The treatment of insomnia has shifted over time, with a growing emphasis on nonpharmacologic therapies as a first-line intervention and the leveraging of technology to aid in the dissemination of these therapies. With this evolution, the definition of insomnia has changed to reflect a common treatment pathway. As pharmacologic treatment options have increased, so has concern about the dangerous short-term and long-term adverse effects of these treatment options.

ESSENTIAL POINTS:

Insomnia is a common disorder, frequently overlapping with other neurologic and psychiatric disorders, which can cause significant distress and disruption to patients' lives. Nonpharmacologic therapies are highly effective and are now considered first-line treatments. Although efficacy is variable, numerous pharmacologic interventions are available, and many options come with considerable concern about adverse effects, particularly in populations over 65 years old.

KEY POINTS

- A diagnosis of chronic insomnia is defined as difficulty falling asleep or maintaining sleep three or more times per week in conjunction with at least 3 months of associated daytime dysfunction.
- Insomnia in pediatric populations often presents with inappropriate sleep-onset associations or limit-setting.
- Insufficient sleep syndrome, like insomnia, is characterized by reduced sleep time; however, with insufficient sleep syndrome sleep latency is typically short and sleep efficiency is high.
- While not necessary for a diagnosis of insomnia, a sleep study may be recommended to evaluate for suspected comorbid sleep apnea.
- Examples of insomnia perpetuating factors include excessive time in bed, an irregular sleep-wake schedule, rumination or excessive worry about sleep or daytime performance, unhelpful beliefs about sleep, and an overreliance on substances to help with sleep or alertness.
- Insomnia is characterized by a state of global hyperarousal, which is reflected in the underlying pathophysiologic changes associated with the disorder.
- Polysomnography is not indicated for insomnia evaluation unless a clinical suspicion exists for comorbid sleep-related breathing or movement disorders.
- Cognitive behavioral therapy for insomnia is a time-limited multimodal therapy involving the common core principles of sleep restriction, stimulus control, and cognitive and relaxation training.
- Cognitive behavioral therapy for insomnia alone or in combination with medication is more effective for insomnia than medication alone.
- Most US Food and Drug Administration (FDA)-approved medications for insomnia work via the modulation of $GABA_A$ receptors, which are targets of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter for the central nervous system.

- Benzodiazepines are not recommended for older adults due to the increased risks of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes.
- Given their action on orexin (hypocretin), dual orexin receptor antagonists have the potential to induce narcolepsylike symptoms, including sleep paralysis and hypnagogic and hypnopompic hallucinations, which occur in less than 1% of patients.
- Low doses of mirtazapine and doxepin appear highly selective for brain histamine 2 receptors, more so than even the antihistamine medications diphenhydramine and hydroxyzine.
- Given the lack of FDA regulation of exogenous melatonin, there is heterogeneity of doses across and within brands, with actual pill contents that vary from 83% less to nearly 500% more melatonin than advertised.
- Digital cognitive behavioral therapy for insomnia shows promise as an efficient and cost-effective way of delivering therapy to a large number of people, although efforts to increase access to care for individuals with limited access to computers or smartphones are still needed to prevent worsening a digital divide.
- Consumer sleep technologies may increase awareness of sleep health and sleep disorders, although they may contribute to excessive worry about sleep and should not be used as diagnostic tools by themselves.

ARTICLE 10: SLEEP DISORDERS IN PATIENTS WITH NEUROLOGIC DISEASE

Joyce K. Lee-Iannotti, MD. Continuum (Minneap Minn). August 2023;
29 (4 Sleep Neurology):1188-1204.

ABSTRACT

OBJECTIVE:

This article provides an overview of the growing body of evidence showing bidirectional relationships between sleep and various neurologic disorders.

LATEST DEVELOPMENTS:

Mounting evidence demonstrates that disrupted sleep can negatively impact various neurologic disease processes, including stroke, multiple sclerosis, epilepsy, neuromuscular disorders including amyotrophic lateral sclerosis, and headache syndromes. Abnormal sleep can also be a precursor to Alzheimer disease and neurodegenerative disease states such as Parkinson disease and dementia with Lewy bodies. Interventions to improve sleep and treat obstructive sleep apnea may play a vital role in preventing neurologic disease development and progression.

ESSENTIAL POINTS:

Sleep disorders are common among patients with neurologic disorders. To provide comprehensive care to patients with neurologic conditions, neurologists must ask patients about sleep issues that may warrant further diagnostic testing, treatment, and sleep medicine referral when indicated.

KEY POINTS

- Sleep apnea is a well-established independent risk factor for both initial and recurrent strokes.
- Almost three-quarters of people with stroke have poststroke sleep apnea.
- Obstructive sleep apnea has also been linked to individual risk factors for stroke, including diabetes, hypertension, and atrial fibrillation.
- Untreated sleep apnea can increase the risk of recurrent cerebrovascular events.
- Screening for sleep apnea in stroke patients remains underutilized, indicating a need for greater awareness about obstructive sleep apnea as a risk for recurrent strokes.

- The Whitehall II study showed that subjects between 50 and 60 years old who slept 6 hours or less per night, compared with those who slept 7 hours or more per night, had a 30% increased risk of dementia, independent of socioeconomic, behavioral, cardiometabolic, and mental health factors.
- Irregular sleep-wake rhythms and circadian rhythm misalignment may precede cognitive decline and the onset of Alzheimer disease by decades.
- Decreased slow-wave sleep and rapid eye movement (REM) sleep has been associated with abnormal brain accumulation of amyloid-β and tau proteins.
- The relationship between Alzheimer disease and obstructive sleep apnea is directly moderated by apolipoprotein E (*APOE*) ε4 status and body mass index, with cognitive decline being more rapid in *APOE* ε4 allele carriers and those with higher body mass index.
- Light therapy is a potential nonpharmacologic treatment for sleep disturbance in the setting of Alzheimer disease, with preliminary studies demonstrating that timed light exposure can consolidate and improve nocturnal sleep efficiency, increase daytime wakefulness, and reduce evening agitation associated with sundowning.
- REM sleep behavior disorder is common in patients with Parkinson disease and is now considered a prodromal risk factor for the development of α-synucleinopathies including Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.
- Fatigue is the leading cause of decreased quality of life and affects up to 90% of patients with multiple sclerosis.
- Hypothalamic lesions on MRI can correlate with narcolepsy symptoms in people with multiple sclerosis and neuromyelitis optica spectrum disorder.
- Patients with neuromuscular disease are at high risk for both obstructive and central sleep apnea.
- People with neuromuscular or chest wall disorders may undergo in-laboratory polysomnography with transcutaneous carbon dioxide monitoring to confirm sleep-related hypoventilation and hypercapnia, or they may be empirically treated with settings adjusted based on response and arterial blood gas measurements.
- Sleep-related seizures more commonly occur in the "lighter" stages of non-REM sleep (N1, N2), with REM sleep being protective.
- Sleep disruption has been shown to increase seizure frequency.
- Vagus nerve stimulation therapy may induce obstructive sleep apnea in patients, so careful preimplantation and postimplantation obstructive sleep apnea screening is important.
- Sleep apnea should be screened and treated appropriately in patients with headaches.
- There was a dramatic increase in sleep disorders during the COVID-19 pandemic, including insomnia, daytime hypersomnia, sleep-disordered breathing, and REM sleep behavior disorder.

ARTICLE 11: SLEEP DISORDERS IN CHILDHOOD

Althea Robinson Shelton, MD. Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1205–1233.

ABSTRACT

OBJECTIVE:

This article provides a comprehensive review of pediatric sleep disorders including the clinical features, diagnosis, and treatment of sleep-disordered breathing, insomnia, parasomnias, restless sleep disorder, restless legs syndrome, narcolepsy in childhood, and Kleine-Levin syndrome.

LATEST DEVELOPMENTS:

Our understanding of pediatric sleep pathophysiology continues to evolve, and diagnostic and treatment modalities have expanded. A low-sodium oxybate formulation was approved in July 2020 in the United States to treat cataplexy and excessive daytime sleepiness in patients 7 years old and older with narcolepsy. A validated pediatric hypersomnolence survey for pediatric narcolepsy and idiopathic hypersomnia with high sensitivity, specificity, and interrater reliability is now available.

ESSENTIAL POINTS:

The clinical presentation, diagnostics, and treatment of children with sleep disorders differ from those of adults. Untreated sleep disorders in childhood can lead to adverse physical and psychological consequences in adults. Correctly diagnosing and treating sleep disorders in youth can prevent a significant burden of disease in adulthood.

KEY POINTS

- The characteristic sleep change in adolescence is the natural tendency to delay sleep onset and wake times due to changes in circadian rhythm, largely driven by the release of melatonin later in the night.
- Lack of N3 and rapid eye movement (REM) sleep is associated with increased insulin resistance, and shorter sleep duration is associated with higher blood pressure in childhood.
- Screening for sleep-disordered breathing should be included in general pediatric and multidisciplinary assessments of childhood learning difficulties.
- Children and adolescents with obstructive sleep apnea should have regular blood pressure monitoring to identify those at higher risk of continued hypertension into adulthood.
- In addition to adenotonsillectomy, surgical options for obstructive sleep apnea include lingual tonsillectomy, supraglottoplasty, posterior midline glossectomy, and palatopharyngoplasty.
- Drug-induced sleep endoscopy is a method that can help visualize the level of collapse in the upper airway while the patient is sedated, which likely replicates upper airway physiology during sleep.
- Midface hypoplasia from the long-standing pressure of the mask on growing facial structures is a possible adverse effect of positive airway pressure therapy in children. Thus, it is essential to perform regular mask fittings.
- Central sleep apnea is rare in healthy children. The most common cause of central sleep apnea in otherwise healthy children is Chiari malformation.
- Behavioral interventions should always be the first line in the treatment of pediatric insomnia.
- A family's culture and socioeconomic status should be considered when initiating behavioral strategies for the management of insomnia.
- Non-REM parasomnias such as sleepwalking, confusional arousals, and sleep terrors occur in the first third of the night.
- Conditions that cause sleep fragmentation, such as obstructive sleep apnea and excessive periodic limb movements of sleep, noise, fever, stress, and anxiety, and conditions that increase N3 sleep, such as sleep deprivation and sedatives (eg, zolpidem), can trigger non-REM parasomnia.
- For the diagnosis of definite restless legs syndrome (RLS), children must be able to describe symptoms in their own words. Age-appropriate descriptors are encouraged.
- Low iron stores are the leading risk factor for RLS. Serum ferritin levels lower than 50 ng/mL are highly correlated with RLS symptoms.
- Clinical studies demonstrate a correlation between RLS and attention deficit hyperactivity disorder.
- Growing pains are a common mimic of RLS. However, growing pains are always described as painful and do not present with the urge to move the legs; the pain is not relieved by movement.
- The pathophysiological model for narcolepsy type 1 involves autoimmune-mediated destruction of orexin-A (hypocretin-1)-containing neurons in the lateral hypothalamus.
- In children, cataplexy can occur without an external emotional trigger.

- Body weight may increase quickly and prominently at disease onset in children with narcolepsy.
- Precocious puberty occurs in 17% of pediatric patients with narcolepsy compared to 1.9% in children with obesity who do not have narcolepsy.
- Behavioral and mental health screening should be a part of regular care for patients with pediatric narcolepsy.
- Nonmedical conservative management such as scheduled napping enhances pharmacologic management of narcolepsy. To reap the greatest benefit, consistent bedtime and sufficient sleep duration should be paired with scheduled napping.
- The key features of Kleine-Levin syndrome are hypersomnia, cognitive dysfunction, and a feeling of derealization. Hyperphagia and hypersexuality occur together in about 45% of cases.

ARTICLE 12: SLEEP DEPRIVATION AND ITS CONSEQUENCES

Oleg Y. Chernyshev, MD, PhD. Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1234–1252.

ABSTRACT

OBJECTIVE:

This article reviews the clinical, cognitive, behavioral, and physiologic consequences of sleep deprivation in relation to general neurology practice.

LATEST DEVELOPMENTS:

Despite being one of the most common sleep problems in modern society, the role of sleep deprivation is underrecognized and underestimated in clinical medicine and general neurology practice. The recognition, diagnosis, and management of sleep deprivation in neurologic practice have only recently received close attention. The consequences of sleep deprivation involve all aspects of general neurology practice, including individuals with neurologic disease, neurologists, communities, and health care systems. The identification and timely management of sleep deprivation symptoms may help to improve symptoms of underlying primary neurologic disorders.

ESSENTIAL POINTS:

This article emphasizes complexities related to the identification and evaluation of sleep deprivation in general neurology practice and describes the consequences of sleep deprivation. By recognizing sleep deprivation in patients with neurologic conditions, the neurologist can provide comprehensive care and contribute to improved clinical and neurologic outcomes.

KEY POINTS

- Sufficient sleep is determined by the adequate duration, continuity, regularity, stability, and quality of sleep.
- Sleep fragmentation refers to disrupted sleep continuity and stability per 24-hour period for one or more consecutive nights.
- Sleep deprivation from either insufficient sleep time or sleep disorders is a significant public health problem affecting 50 to 70 million Americans.
- The prevalence of sleep deprivation is elevated in professional environments with long or extended work hours, rotating or shift work, and increased job-related stress.
- Sleep deprivation impairs functions mediated by the prefrontal cortex that affect working memory and attention.

- The shorter the sleep duration, the greater the cognitive deficits.
- During persistent sleep deprivation, both daytime sleepiness and cognitive impairments continue to progress unless planned sleep occurs.
- Chronically sleep-deprived individuals are often unaware of their increasing cognitive deficits and underestimate the negative impact of sleep deprivation on cognition and performance.
- The impairment of cognitive psychomotor performance after 17 hours of sustained wakefulness is equivalent to the effect produced by a blood alcohol concentration of 0.05%, and after 24 hours of extended wakefulness it is equivalent to a blood alcohol concentration of 0.1% (exceeding the legal limit for driving in most states).
- Sleep deprivation is linked to stress and anxiety disorders, and acute sleep deprivation may cause short-term remission of major depressive disorder.
- Increasing the duration of recovery sleep for one night following chronic sleep deprivation leads to progressive improvements in neurobehavioral performance, but some deficits persist even after 10 hours of recovery sleep.
- Sleep plays a vital neuroprotective role in clearing the toxic metabolites produced in the brain via the glymphatic system. During sleep, CSF flows more profusely, significantly increasing the elimination of toxic substances from neurons and intercellular spaces.
- When sleep is restricted, the glymphatic system does not have enough time to fulfill its function of removing toxins and misfolded proteins.
- The clearance of brain interstitial solutes and wastes is one of the most important biological processes underlying the restorative function of sleep.
- Sleep deprivation (<5 to 6 hours per night) is associated with decreased pain tolerance, increased pain sensitivity, and hyperalgesia.
- The selective disruption of non–rapid eye movement (non-REM) slow-wave sleep causes a lowering of the pain threshold and promotes pain sensitivity. Extended sleep duration (7 to 9 hours per night) is associated with reduced pain symptoms.
- Sleep deprivation exacerbates stroke pathophysiology by increasing the expression of growth-inhibiting genes, neuroinflammation, and oxidative stress.
- Sleep deprivation and sleep disorders may affect epilepsy by reducing seizure threshold and facilitating seizure occurrence.
- The epileptiform discharges and facilitated propagation of seizure activity from the epileptic focus readily occur during the synchronized pattern of non-REM sleep, specifically during the N2 stage.
- Migraine and sleep have a reciprocal relationship. Sleep deprivation is a common trigger for both episodic and chronic migraine with and without aura and for tension-type headache.
- The sleep-associated occurrence of attacks in cluster headache can lead to sleep deprivation and contribute to reduced quality of life.
- Sleep deprivation impairs the glymphatic and aquaporin-4 channel systems, which results in the aggregation of β-amyloid and tau proteins and accelerates the formation of amyloid plaques and neurofibrillary tangles.
- Sleep deprivation changes homeostatic sleep drive at the molecular levels of gene transcription, translation, and protein synthesis, resulting in elevated cortical expression of the period circadian regulator 1 and 2 (*PER1* and *PER2)* clock genes, which are also associated with disorders observed in circadian rhythm disruption.
- Sleep deprivation affects the signaling mechanisms that regulate transcription and translation processes involved in memory.
- The effects of sleep disruption on sympathetic activity, glucose metabolism, and inflammation may lead to adverse cardiovascular effects.
- Acute sleep deprivation is associated with increases in heart rate and blood pressure and a reduction in heart rate recovery.
- Sleep deprivation increases blood pressure, heart rate, catecholamine activity, and sympathetic surge, which impairs the physiologic “nocturnal dip” in blood pressure during non-REM sleep.

- Sleep deprivation decreases intrinsic ventilatory drive to hypoxic and hypercapnic states by causing decreased chemoreceptor sensitivity to oxygen and carbon dioxide. Sleep deprivation reduces respiratory motor output, weakens inspiratory muscle strength, and impairs respiratory motor plasticity (ie, inspiratory drive-in response to hypoxia).
- Sleep deprivation is associated with temperature dysregulation, which leads to temperature elevation during the initial stages of sleep deprivation followed by a decline in body temperature.
- Sleep deprivation is linked to impaired fasting glucose, sustained hyperglycemia, low glucose tolerance, elevated insulin resistance, and diabetes mellitus, as well as persistently elevated levels of catabolic immunosuppressive hormones and suppressed levels of anabolic, immunofacilitatory hormones.
- Sleep deprivation is associated with an increase in excessive intake of food and weight gain.
- Increases in central obesity and metabolic syndrome, higher levels of fasting glucose, blood pressure, and triglycerides, and a reduction in the level of high-density lipoprotein cholesterol are all seen in the setting of sleep deprivation.
- Sleep deprivation is associated with a decreased vaccine immune response and a higher risk of developing pneumonia or an upper respiratory infection following rhinovirus exposure.
- Data from numerous studies indicate that patient-ventilator mismatch, rather than any given ventilator mode, is most responsible for sleep disturbance.
- Sleep deprivation is very common among medical students, residents, and practicing physicians, leading to health problems, medical errors, professional burnout, marital problems, motor vehicle accidents, depression, suicidality, and addiction.
- Sleep deprivation in night-shift workers and medical practitioners leads to significant increases in blood pressure, heart rate, heart contractility, and stress hormone secretion.
- Fragmented and insufficient sleep has been hypothesized as a potential mechanism that promotes burnout.

ARTICLE 13: IMPLICATIONS OF SLEEP HEALTH POLICY: DAYLIGHT SAVING AND SCHOOL START TIMES

Karin G. Johnson, MD, FAAN, FAASM; Beth A. Malow, MD, MS, FAAN.
Continuum (Minneap Minn). August 2023; 29 (4 Sleep Neurology):1253–1266.

ABSTRACT

Two proposed public policies, ending seasonal clock change with a transition to permanent Standard Time and moving middle school and high school start times later, are population-based initiatives to improve sleep health. Daylight Saving Time and early school start times are associated with reduced sleep duration and increased circadian misalignment, the effects of which impact not only long-term health outcomes including obesity, cerebrovascular and cardiovascular disease, and cancer, but also mental health, academics, workforce productivity, and safety outcomes. This article highlights studies that led to the endorsement of these public policies by multiple scientific and medical organizations. Neurologists should advocate at the state and federal levels and educate the population about the importance of sleep health.

KEY POINTS

- The four elements of healthy sleep are duration, quality, timing, and regularity.
- Circadian rhythms primarily align to solar time, or the time when the sun is overhead at noon.
- Social jet lag is the difference between sleep timing on school or workdays and free days.
- Chronotype, or preference for sleep timing, is measured by the midpoint of sleep on free days.

- Social jet lag is greatest between ages 10 and 17 years.
- The spring clock transition from Standard Time to Daylight Saving Time is associated with more negative effects than the fall transition from Daylight Saving Time to Standard Time.
- Short-term effects of clock transitions do not equate to the long-term effects of permanent Daylight Saving Time or permanent Standard Time.
- Seasonal depression rates are highest during permanent Daylight Saving Time and lowest during permanent Standard Time.
- Motor vehicle crash rates are higher in locations with later sunrises and sunsets.
- Later school start times are associated with higher attendance, higher grades, and better test scores.
- The American Academy of Neurology (AAN) and over 90 medical, scientific, safety, education, and religious groups have endorsed permanent Standard Time.
- Middle schools and high schools should start classes after 8:30 AM.

Issue Overview

Sleep Neurology, Volume 29, Number 4, August 2023

Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue, participants will be able to:

- Identify and describe basic concepts related to brain structures involved in the regulation of wakefulness and sleep physiology, and their interactions with pharmacologic interventions and circadian rhythms
- Evaluate patients with sleep-related symptoms, the association between neurologic conditions and sleep disorders, and testing modalities to diagnose and monitor common sleep disorders
- Identify common presentations of narcolepsy and idiopathic hypersomnia and apply evidence-based clinical guidelines for the treatment of patients with central disorders of hypersomnolence
- Describe the epidemiology, pathophysiology, clinical presentation, and diagnosis and treatment options for obstructive sleep apnea
- Describe parasomnias that arise from rapid eye movement sleep, including rapid eye movement sleep behavior disorder and its diagnosis, management, and association with neurodegenerative diseases
- Recognize the clinical characteristics, classification, and treatments of parasomnias that occur in non–rapid eye movement sleep
- Discuss the evaluation and management of restless legs syndrome and other sleep-related movement disorders
- Describe the ubiquity of physiologic clocks in biological functions and the impact of circadian rhythm sleep-wake disorders on neurologic conditions and overall health, and convey the importance of a healthy circadian rhythm to patients and advise them on management strategies
- Describe the diagnosis and management of insomnia, including the role of pharmacologic and nonpharmacologic therapies and the growing use of technology within this field
- Elucidate the growing body of evidence showing a bidirectional relationship between sleep and multiple neurologic disease states
- Describe the pathophysiology, clinical presentation, diagnosis, and management of common pediatric sleep disorders
- Identify, define, and describe the signs and symptoms of sleep deprivation and its main consequences, and apply this knowledge to neurologic practice

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Sleep Neurology issue covers the following core competencies:

- Patient Care and Procedural Skills
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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