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CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Sleep-Related Problems in Neurologic Diseases

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There is a strong association between sleep-related problems and neurologic diseases. Neurologic diseases of the CNS can directly cause sleep problems when sleep-wake mechanisms associated with the ascending reticular activating system are involved. The major sleep disorders associated with neurologic problems are outlined in the *International Classification of Sleep Disorders, 2nd edition*, as hypersomnias of central origin, sleep-related breathing disorders, the insomnias, circadian rhythm sleep disorders, sleep-related movement disorders, parasomnias, and sleep-related epilepsy. In a patient with CNS disease and excessive sleepiness, sleep-related breathing disorders should be a first concern, given the known association between obstructive sleep apnea (OSA) and cerebrovascular disease and the potential confounding effects that OSA might have on an otherwise compromised ischemic CNS penumbra. A basic knowledge of the anatomy and physiology of the sleep-wake mechanisms provides a rationale for pharmacologic intervention. Nonpharmacologic treatments are also important, especially when sleep-related breathing disorders are a concern. In addition, as patients with neurologic diseases are often prone to the adverse effects of many medications, the specific treatment regimen for any given individual should always include good sleep hygiene practices that use cognitive behavioral therapy.

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Abbreviations: CPAP = continuous positive airway pressure; DRG = dorsal respiratory group; NPPV = noninvasive positive pressure ventilation; OSA = obstructive sleep apnea; PLMS = periodic limb movements during sleep; PSG = polysomnography; RBD = rapid eye movement sleep behavior disorder; REM = rapid eye movement; RLS = restless legs syndrome; SCN = suprachiasmatic nucleus; TBI = traumatic brain injury; VRG = ventral respiratory group

The National Sleep Foundation "Sleep in America" poll from 2002 reported that 66% of adults with excellent or good health experienced at least one symptom of a sleep disorder (difficulty falling asleep, waking a lot during the night, waking up too early and not being able to get back to sleep, waking up feeling unrefreshed, snoring, unpleasant tingling feelings in the legs, or pauses in breathing) a few nights a week or more.[1] This number increased to 93% for individuals with fair or poor health. In addition, sleepiness interfering with daily activities was reported by 33% of those who rated their overall health as either excellent, very good, or good. This degree of sleepiness was found in 55% of respondents with fair or poor health. As such, it is not surprising that there is a strong association between sleep-related problems and poor health secondary to neurologic disease. Given the large numbers of patients with neurologic disease, successfully addressing concomitant sleep problems can improve quality of life for a significant portion of our general population, potentially reducing morbidity and mortality in many cases.

The clinical approach to any patient with a sleep problem must include a full sleep history. A sleep history is mandated for accurate diagnosis, after which appropriate therapeutic interventions can then be instituted. The sleep history is also used to justify the use of formal sleep studies, including overnight polysomnography (PSG). Although PSG is not necessary

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in working up most sleep disorders, it is routinely indicated when confirming the diagnosis of some hypersomnias of central origin, such as narcolepsy, sleep-related breathing disorders, and the parasomnia known as the rapid eye movement (REM) sleep behavior disorder (RBD).

Hypersomnias of Central Origin

Hypersomnia is a primary complaint of excessive sleepiness. Neurologic problems affecting the CNS frequently directly cause dysfunction of central waking mechanisms (Table 1).[2] Hypersomnia has been reported with a variety of neurodegenerative and genetic disorders, stroke, head trauma, encephalitis, and brain tumors.[2-6] Wakefulness mechanisms that function through the ascending reticular activating system involve the brainstem, hypothalamus, basal forebrain, and the thalamus (Fig 1).[3,4,6-8] The chemical definition of the neurotransmitters associated with these mechanisms has led to effective pharmacologic treatments using drugs that mimic the structure of the endogenous neurotransmitters (Fig 2).[3,4,6]

Hypersomnia Due to Medical Condition

Neurodegenerative Disorders: Neurodegenerative disorders are typified by Parkinson disease and include Alzheimer disease and frontotemporal and Lewy body dementia.[3] In Parkinson disease, sleepiness may result from degeneration of dopaminergic neurons in the substantia nigra and cholinergic cells in the basal forebrain. Petit et al[9] have suggested two drug regimens for sleepiness in a variety of degenerative disorders: modafinil, 100 mg qAM, increasing as needed in 100-mg increments every 5 to 7 days, in a bid dosing schedule (morning and noon); and methylphenidate, an initial dose of 2.5 mg, increasing by 2.5-mg to 5-mg increments every 3 to 5 days as needed, using a bid dosing schedule.

Table 1—*The Major Sleep-Related Problems in Neurologic Disease as Outlined in the ICSD-2*

Hypersomnias of central origin
Hypersomnia due to medical condition
Narcolepsy due to medical condition
Recurrent hypersomnia
Kleine-Levin Syndrome
Sleep-related breathing disorders
Sleep apnea
Sleep-related hypoventilation/hypoxemic syndromes
Insomnia due to medical condition
Circadian rhythm sleep disorder due to medical condition
Sleep-related movement disorder
Restless legs syndrome and periodic limb movements in sleep
Parasomnias
REM sleep behavior disorder
Sleep-related epilepsy

ICSD-2 = *International Classification of Sleep Disorders, 2nd edition;* REM = rapid eye movement. (Modified with permission from American Academy of Sleep Medicine.[2])

Stroke: The prevalence of hypersomnia in acute ischemic stroke is estimated at 22%.[10] Hypersomnia has been reported following stroke of the pontine tegmental reticular formation, hypothalamus, and thalamus.[5,11] Improvements in hypersomnolence with hypothalamic/thalamic infarctions have been reported using 200 mg of modafinil.[11] Reduced sleepiness using methylphenidate (5-30 mg/d) and levodopa (100 mg/d) has led to overall clinical improvements during stroke rehabilitation.[12,13] Improvements in sleepiness, apathy and behaviors counterproductive to good sleep have also been reported using 20 to 40 mg/d of bromocriptine.[14]

Head Injury: Sleepiness is common after traumatic brain injury (TBI) and can occur in severe cases associated with coma and even after mild head injuries.[15] The hypothesis that variable CNS wakefulness centers can be affected in TBI has been supported by a study wherein low cerebrospinal fluid (CSF) hypocretin-1 levels were found in 25 of 27 patients the first few days after TBI.[16] The chemical structures of CNS stimulant medications like amphetamines compares similarly with the endogenous catecholamines norepinephrine and dopamine that are used by CNS waking systems. In this regard, amphetamines have been shown to reduce sleepiness in some individuals recovering from posttraumatic coma.[15]

Genetic Disorders: Neurologic genetic disorders associated with hypersomnolence include Niemann-Pick type C disease and myotonic dystrophy.[17,18] Niemann-Pick type C disease is a lipid storage disease that can present in infants, children, and adults.[17] Hypersomnolence can result from accumulations of unesterified cholesterol and sphingolipids in the hypothalamus that lead to a deficiency of hypocretin/orexin (a wake-promoting neuropeptide).[17,19] Myotonic dystrophy (dystrophia myotonica type 1) is caused by a mutation in the dystrophia myotonica-protein kinase gene.[18,20] In this disorder, dysfunction of the hypothalamic hypocretin/orexin system and loss of serotonin in the dorsal raphe nucleus (a brainstem "wakefulness" center) may lead to sleepiness.[18,20,21]

Narcolepsy Due to Medical Condition

Narcolepsy with cataplexy (sudden loss of muscle tone precipitated by strong emotion) is genetically associated with the human leukocyte antigen subtype DQB1*0602 and an intrinsic loss of hypothalamic neurons containing the neuropeptide hypocretin/orexin with low CSF levels of hypocretin-1, which allows the inappropriate onset of REM/"paralyzed"/"dream"

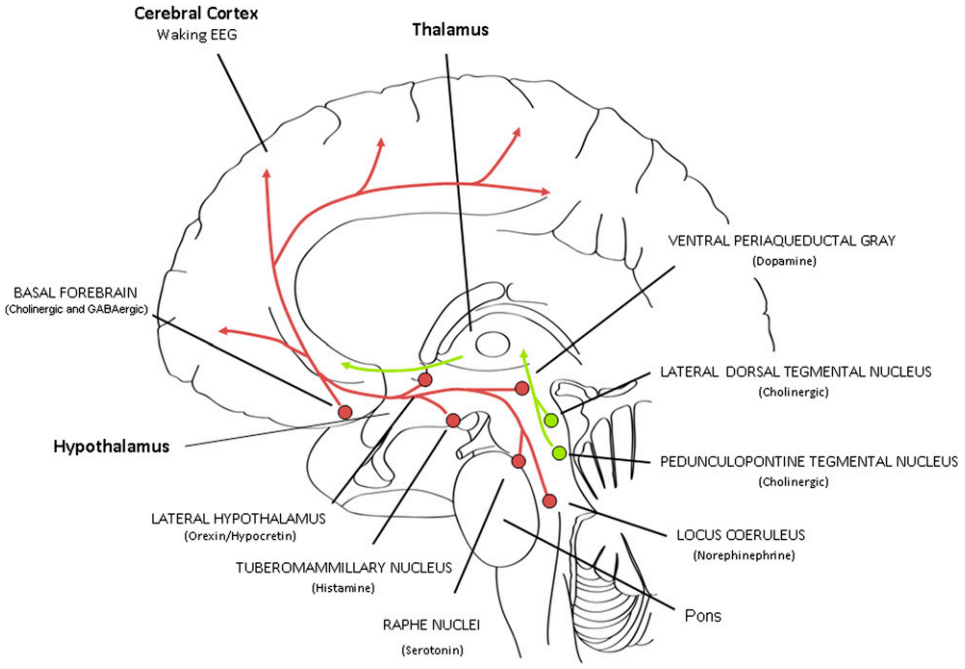

FIGURE 1. Basic wake systems. This diagrammatic representation of the brain/brainstem in the parasagittal plane shows the very basic structures and mechanism hypothesized to be involved in the generation of wakefulness in humans. There are two ascending independent waking pathways that travel through the pontomesencephalic junction that eventually lead to diffuse cortical projections: (1) the neuronal tracts and nuclear areas in red define a ventral system through the hypothalamus (involving hypothalamic nuclei in the tuberomammillary nucleus and the lateral hypothalamus [LH]), which relays to cholinergic and GABA basal forebrain (BF) cells and the cerebral cortex; and (2) the neuronal tracts and nuclear areas in green define a dorsal thalamic route that leads to stimulation of thalamic relay, nonspecific midline, and intralaminar nuclei (while inhibiting the reticular nucleus of the thalamus). The orexin/hypocretin neurons in the LH reinforce the waking activity of all these nuclei and directly innervate the BF (the nucleus basalis, diagonal band of Broca, and medial septal nuclei) and the cerebral cortex. In the BF there are cholinergic cells that excite cortical pyramidal neurons and GABAergic cells that inhibit cortical inhibitory interneurons (thus disinhibiting the cortex). Both groups are active during wakefulness and rapid eye movement (REM) sleep, but relatively inactive (or at least less active) during the non-rapid eye movement (NREM) stages of sleep. GABA = γ-aminobutyric acid. (Adapted with permission from Saper et al.[8])

sleep phenomena described as the classic pentad of symptoms: excessive daytime sleepiness (often with sleep attacks), cataplexy, sleep paralysis (hypnagogic when going to sleep, hypnopompic upon awakening), hypnagogic hallucinations, and nocturnal sleep disruption (insomnia).[4] In a review of 116 subjects, inherited neurologic disorders (n = 38), tumors (n = 33), and head trauma (n = 19) were the most common causes of symptomatic narcolepsy. Other specific causes included multiple sclerosis (n = 10), vascular disorders (n = 6), encephalitis (n = 4), inherited degenerative diseases (n = 3), dementia (n = 1), and acute disseminated encephalomyelitis (n = 1).[22]

Sleepiness is associated with damage to lateral hypothalamic orexin/hypocretin cells and CSF hypocretin-1 levels ≤ 110 pg/mL (Fig 3).[7] Resolution of symptomatic narcolepsy has followed normalization of CSF hypocretin-1 levels in the treatment of multiple sclerosis and disseminated encephalomyelitis.[22,23] In a case of primary CNS B-cell lymphoma, initially undetectable CSF hypocretin-1 levels normalized to 244 pg/mL, with a resolution of sleepiness and cataplexy after treatment, which included IV/intrathecal methotrexate and corticosteroids.[24]

Recurrent Hypersomnia; Kleine-Levin Syndrome

The Kleine-Levin syndrome, originally described in male patients, is characterized by periods of hypersomnia, hyperphagia, and encephalopathy that can last weeks and can recur up to 10 times a year.[6] These episodes tend to improve over a 4-year period and rarely continue after 10 to 20 years, and other than encephalopathy, the physical examination and brain MRI are usually normal.[6] Although single photon emission CT scans suggest thalamic blood flow is reduced, case studies with encephalitis, stroke, and head injury have reported low CSF orexin/hypocretin levels, which support autopsy evidence indicating hypothalamic injury.[6,25] Stimulants may improve sleepiness, and lithium (especially in posttraumatic Kleine-Levin syndrome) may reduce the frequency, severity, and

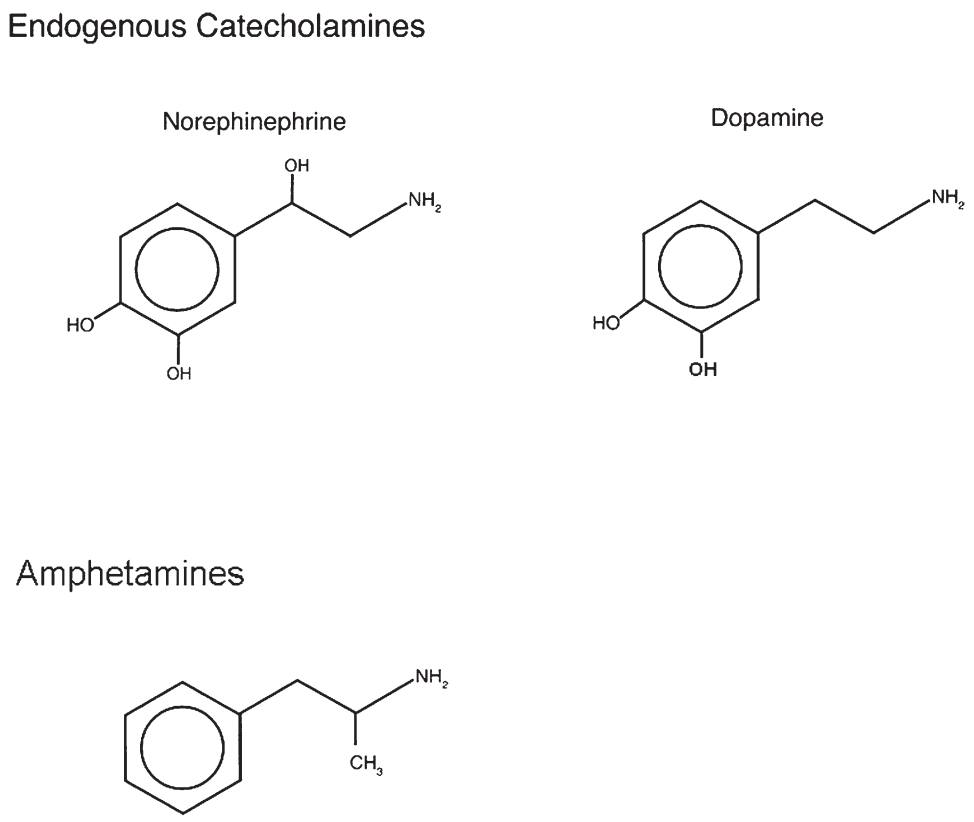

FIGURE 2. The chemical structures of central nervous system stimulant medications, such as amphetamine and amphetamine-like stimulants, compares similarly with the endogenous catecholamines norepinephrine and dopamine that are used by the intrinsic central physiologic waking systems. (Adapted with permission from Dyken et al.[6])

length of relapses.[26] In one study, significant reductions in sleepiness were reported using lithium in five of eight patients and carbamazepine in three of eight subjects, whereas modafinil provided a "good response" in four individuals and was "partially effective" in ten.[27]

Sleep-Related Breathing Disorders

Sleep Apnea

Sleep apnea has been associated with stroke, dementia, and encephalitis, especially when there is injury to central respiratory centers.[3,28-31] Automatic respiration (subject to modulation by multiple CNS sites) depends on the medullary respiratory center, which is composed of the dorsal respiratory group (DRG) (the nucleus solitarius) and the ventral respiratory group (VRG) (includes the nucleus ambiguus) (Fig 4).[28,32,33] Central sleep apnea has been documented after stroke involving the nucleus solitarius, presumably due to impairment of inspiratory mechanisms, whereas obstructive sleep apnea (OSA) has been reported after stroke of the VRG, possibly due to isolated damage of the nucleus ambiguus and consequent dysfunction of the vagal motor innervation to the larynx and pharynx.[28] Case studies have also suggested that diffuse CNS injury affecting variable areas of respiratory control can lead to apnea.[31,32]

Routinely, OSA is treated with continuous positive airway pressure (CPAP) therapy, generally delivered through a nasal mask, which acts as a stent to keep the airways open.[2,3,5,6] In critically ill patients, more aggressive therapies include the use of noninvasive positive pressure ventilation (NPPV) with bilevel positive airway pressure and invasive ventilation using endotracheal intubation or tracheostomy.[5,6]

Stroke: Case-control studies show a prevalence of OSA up to 71% in patients with acute stroke, whereas cohort studies suggest OSA is a risk factor for stroke.[28-30,34,35] The American Heart Association and the American Stroke Association Stroke Council have classified sleep disordered breathing as a "Less Well-Documented or Potentially Modifiable Risk Factor" for ischemic stroke.[36]

A prospective study of ischemic stroke compared the 5-year mortality between CPAP vs non-CPAP users.[37] Individuals who did not tolerate CPAP and had an apnea-hypopnea index (the average number of apneas and hypopneas per hour of sleep) >20 showed an increased adjusted risk of mortality (hazard ratio,

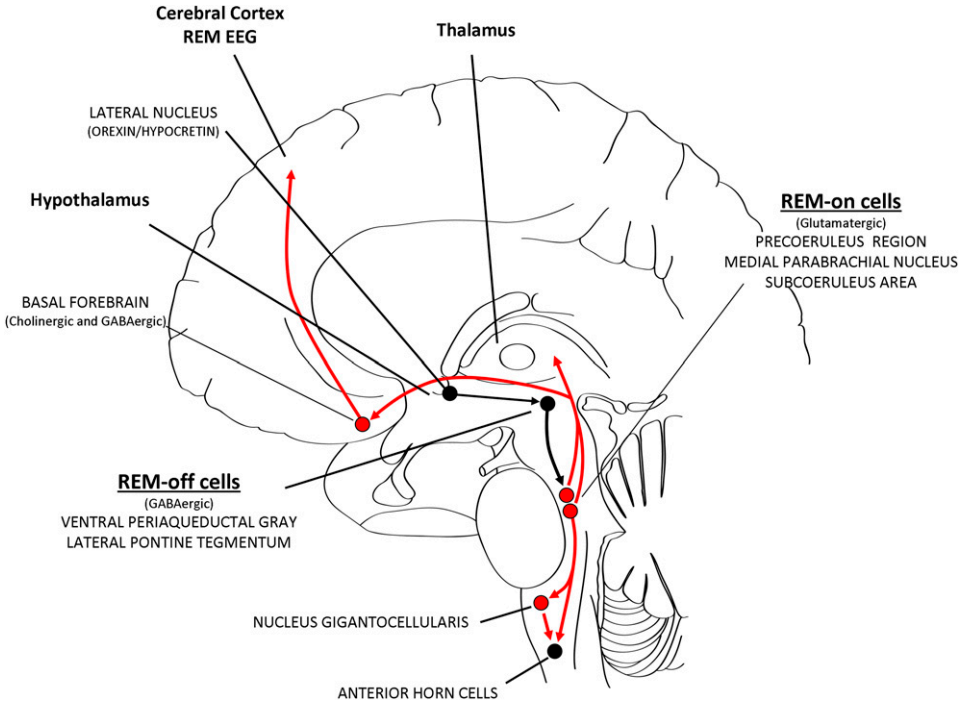

FIGURE 3. This diagrammatic representation of the brain/brainstem in the parasagittal plane shows the very basic structures and mechanism (based upon the recently proposed "Flip-Flop" model of sleep state transitions by Saper et al.[7]) hypothesized to be involved in some cases of symptomatic narcolepsy. The paucity of orexin (hypocretin) cells in the lesioned lateral hypothalamus results in a loss of stimulation of GABAergic REM-off cells in the ventral periaqueductal gray/lateral pontine tegmentum complex, which leads to a disinhibition of the pontine glutamatergic REM-on cells specifically localized precoeruleus region (PCR), the medial parabrachial nucleus (MPBN), and in the subcoeruleus area (SCA; referred to as the SCA in cats and the sublaterodorsal nucleus in rats; not clearly identified in humans). Subsequently, rostrally directed pathways from the PCR, MPBN, and SCA lead to the forebrain (the cerebrum, hypothalamus, and thalamus) producing an REM EEG pattern, whereas caudally directed pathways from the SCA lead to hyperpolarization of spinal cord anterior horn cells (directly and indirectly via the nucleus gigantocellularis), producing the atonia associated with inappropriate REM onset sleep, cataplexy, and sleep paralysis (major symptoms of narcolepsy). Black circles and lines indicate nuclei and neuronal tracts normally inhibited during REM sleep; red circles and lines indicate nuclei and neuronal tracts normally activated during REM sleep. See Figure 1 legend for expansion of other abbreviations.

1.58; 95% CI, 1.01-2.49; $P = .04$) when compared with subjects with moderate to severe OSA who tolerated CPAP. Another study showed that in a supportive environment, patients with stroke and OSA tolerated CPAP well (>4 h per night) with normalization of oxygen saturations despite moderately severe disability on mean motor and cognitive functional independence measures.[38]

Positional OSA (apnea worse in the supine position) is prominent in acute stroke. In a study assessing 55 subjects within 72 h after stroke, 78% were acutely diagnosed with OSA (65% positional), whereas after 6 months the prevalence of OSA dropped to 49% (33% positional).[39] This suggests that OSA can be a transient phenomenon of acute stroke, and positional therapy (avoiding sleeping supine, or sleeping with the head of bed elevated) may be a viable therapeutic option.

Dementia: In dementia, degenerative processes may affect brainstem respiratory centers, as sleep-related breathing disorders are frequently reported.[3] The hypothesis that treating OSA may improve the quality of life in dementia is supported by a randomized double-blind placebo-controlled trial that used CPAP in 52 men and women with mild to moderate Alzheimer disease and OSA.[40,41] Comparison of pretreatment and posttreatment neuropsychologic scores after 3 weeks of CPAP showed significant cognitive improvements.[41]

Encephalitis: One case report diagnosed OSA, with an apnea-hypopnea index of 25.4, during acute viral encephalitis.[31] After aggressive treatment with CPAP, IV acyclovir, and broad-spectrum antibiotics, the patient's stupor-coma resolved, at which time repeat PSG showed complete resolution of OSA, including during REM sleep supine.

Sleep-Related Hypoventilation/Hypoxemia Due to Neuromuscular Disorders

In normal non-REM (NREM) sleep, compared with wakefulness, there is a decrease in minute ventilation,

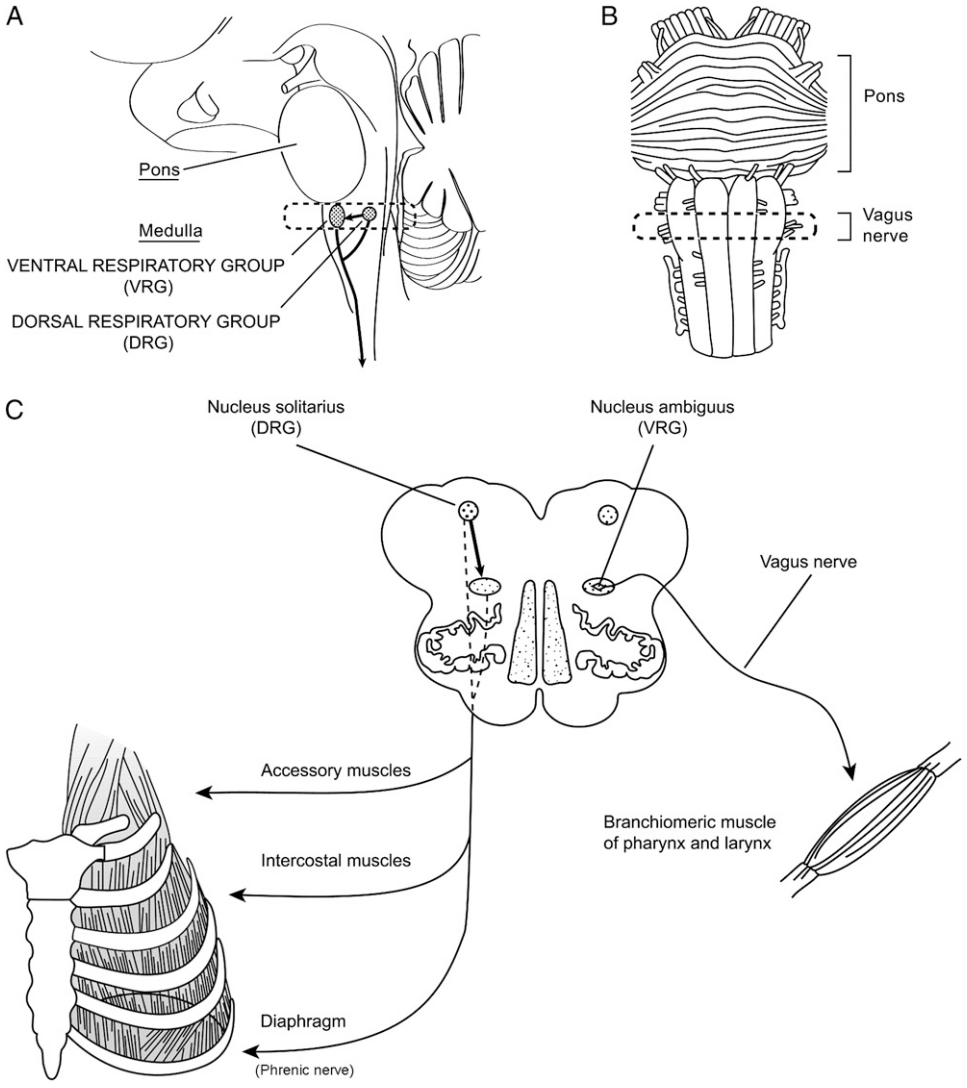

FIGURE 4. A, Schematic of the brain stem in a parasagittal section shows the locations of the DRG and the VRG and their projections to the spinal cord. B, In a basal brain view, vagus nerve rootlets are shown exiting the lateral surface of the medulla. C, In a transverse section of the medulla at a level indicated by the stippled outline in B, projections are shown from the DRG to VRG, with output from both groups to respiratory muscles. The DRG is composed of neurons from the nucleus solitarius, whereas the VRG is composed of the nucleus ambiguus, retrotrapezoid neurons, and the Botzinger and pre-Botzinger complexes. (Adapted with permission from Dyken et al.[33])

tidal volume, and alveolar ventilation, with a progressive increase in $Paco_2$ from 3 to 7 mm Hg, decrease in Pao_2 from 3.5 to 9.4 mm Hg, and decrease in oxygen saturation as measured by pulse oximetry (Spo_2) $\leq 2\%$.[2,42,43] This can exacerbate underlying breathing problems as suggested by a report estimating that $>40\%$ of patients in one neuromuscular clinic suffered from sleep-related breathing disorders.[44] Due to a reduction in contractility of the intercostal, diaphragmatic, and accessory muscles, neuromuscular patients are often unable to maintain a $Paco_2 \leq 45$ mm Hg.[2] The *International Classification of Sleep Disorders, 2nd edition* (ICSD-2) diagnostic criteria for sleep-related hypoventilation/hypoxemia includes PSG or sleeping arterial blood gas that shows any of the following: an Spo_2 during sleep $<90\%$ for >5 min (with a nadir of at least 85%), $>30\%$ of the total sleep time with an $Spo_2 <90\%$, and a sleeping arterial blood gas with a $Paco_2$ that is abnormally high or disproportionately increased relative to waking levels.

It has been reported that patients within all categories of alveolar hypoventilation may benefit from the use of NPPV, but those with neuromuscular diseases have shown the best results with the longest extensions of life.[44] Although no study has really examined whether CPAP might be as effective as NPPV in patients with neuromuscular diseases, a

theoretical advantage of the bilevel positive airway pressure setting (with a relatively higher inspiratory positive airway pressure and a relatively lower expiratory positive airway pressure setting) afforded by NPPV would be to reduce the risk of fatigue-related respiratory arrest from breathing out against too high of an expiratory positive airway pressure. In addition, concerns regarding the anecdotal reports of respiratory arrest associated with overcorrection of elevated $PaCO_2$ levels could be addressed by setting NPPV with a backup demand ventilatory rate.

The American Thoracic Society consensus statement on Duchenne muscular dystrophy recommends annual PSG with continuous CO_2 monitoring once the patient is wheelchair dependent.[45] The American Academy of Neurology practice parameter for amyotrophic lateral sclerosis recommends considering NPPV with symptoms of dyspnea (exertional or when lying supine), marked fatigue, sleepiness, insomnia, and morning headaches and a vital capacity $\leq 50\%$ of predicted.[46] Loss of bulbar muscle tone and difficulty clearing secretions may reduce NPPV tolerance and necessitate invasive ventilation or palliative care.[45-50]

Comparisons between the year before and the first and second years after starting NPPV reveals a significant reduction in the number of hospitalization days in Duchenne muscular dystrophy, from 18 days vs 7 days during the first year after and 2 days during the second year after beginning NPPV.[47] In one study, 46% of the patients with amyotrophic lateral sclerosis tolerated NPPV, but only 30% tolerated it if there were moderate/severe bulbar symptoms.[48] The median duration of survival comparing NPPV-tolerant vs -intolerant patients was 15 months vs 2 months, respectively.

Insomnia Due to Medical Condition

Damage to CNS sleep centers can lead to insomnia (difficulties initiating and/or maintaining sleep) (Fig 5).[3,5,51] In one study of 277 patients with new stroke, 18.7% suffered insomnia acutely, whereas 56.7% developed insomnia within 4 months after

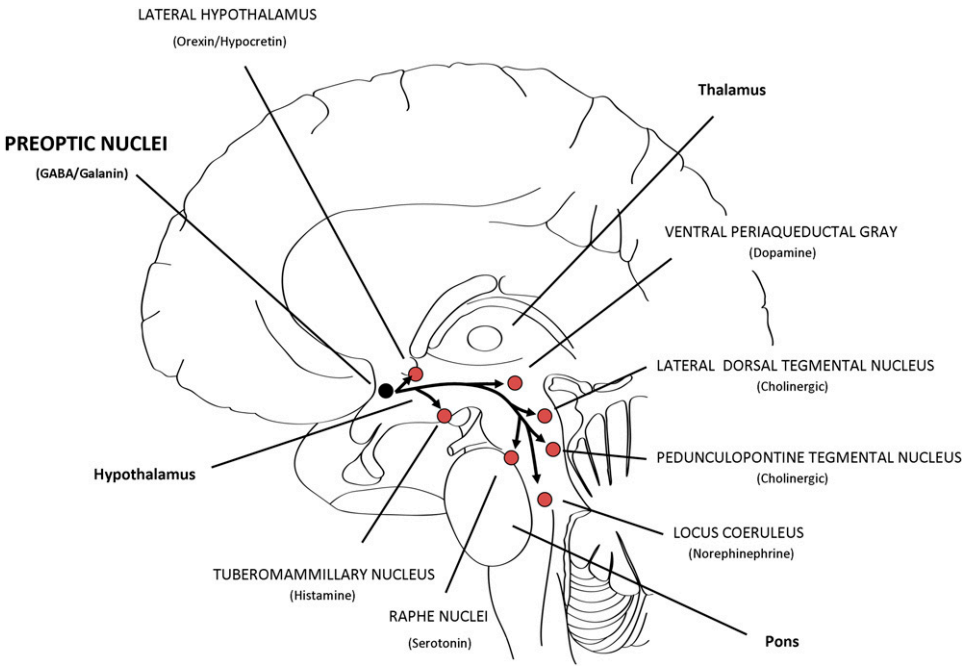

Figure 5. Basic sleep onset systems. Diagrammatic representation of the brainstem in the parasagittal plane showing the proposed structures and mechanism involved in sleep onset. Excited nuclei in the preoptic nuclei of the hypothalamus (the ventrolateral and median preoptic nuclei) use inhibitory neurotransmitters (GABA and galanin) in reciprocal inhibitory relays with waking centers and in direct thalamic projections. In addition, gradual inhibition of REM-off cells that function in part through cholinergic cells of the pedunculopontine tegmental nucleus and lateral dorsal tegmental nucleus complex leads to disinhibition of GABAergic reticular thalamic nuclei that assist in the generation of non-REM sleep through intrathalamic connections to limbic forebrain structures that include the orbitofrontal cortex. Sleep is also facilitated by the solitary tract nucleus, using unknown neurotransmitters, through direct connections with the hypothalamus, amygdala, and other forebrain structures. Serotonergic neurons in the midline (raphe) of the medulla, pons, and mesencephalon of the brainstem help modulate sleep. Black circle and lines indicate inhibitory nuclei and tracts during sleep onset; red circles indicate wakefulness nuclei. See Figure 1 legend for expansion of abbreviations. (Adapted with permission from Saper et al.[8])

stroke.[52] In another study of 336 stroke patients, insomnia was most prevalent with brain stem, frontal lobe, and basal ganglion lesions.[53] The "sleep switch," located in the preoptic area of the hypothalamus, uses the neurotransmitters γ-aminobutyric acid (GABA) and galanin to induce sleep by inhibiting CNS waking centers.[51] Some experts have treated insomnia associated with a variety of neurologic disorders with benzodiazepine receptor agonists with nonselective affinity for the GABA receptor complex (eszopiclone) or selective affinity for the GABA type A receptor (zolpidem and zaleplon).[54] In a patient with a severe neurologic disease like stroke, other factors can contribute to insomnia, including the shock of having a serious illness, adjusting to physical/cognitive limitations, depression, and medication side effects.

Circadian Rhythm Sleep Disorder Due to Medical Condition

The ICSD-2 definition of a circadian rhythm sleep disorder is based upon the existence of a persistent or recurrent sleep disturbance that is due to an alteration of systems that affect the timing of sleep. Nevertheless, to truly be considered a disorder, the problem must lead to a level of insomnia or excessive daytime sleepiness that impairs normal functioning.[2]

Dementia

The classic circadian rhythm disorder known as "sundowning" (excessive daytime sleepiness with nocturnal insomnia, confusion, and agitation) occurs with a variety of degenerative CNS processes, especially Alzheimer disease and multi-infarct dementia, due to a presumed loss of neurotensin- and vasopressin-containing cells in the "biological clock," the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus.[3,55] Daylight is a powerful zeitgeber (external cue) that promotes wakefulness through the retinohypothalamic track by activating a subset of SCN neurons, which subsequently inhibit sleep mechanisms of the paraventricular hypothalamic nucleus (PVN) (Figs 6, 7).[56] Conversely, nighttime darkness disinhibits sympathetic fibers in the PVN, which sequentially stimulate cells in the upper thoracic intermediolateral cell columns, the superior cervical ganglion, and ultimately the pineal gland, to produce the sleep-promoting hormone melatonin (Fig 8).[56,57]

Light therapy is often considered, as during the day sundowning is worse when illumination is low. A 14-week trial involving nursing home residents found that by increasing exposure to outdoor sunlight with physical activity and improved nighttime sleep hygiene practices there was a reduction in sundowning.[58] Satlin and colleagues[59] treated 10 patients with Alzheimer

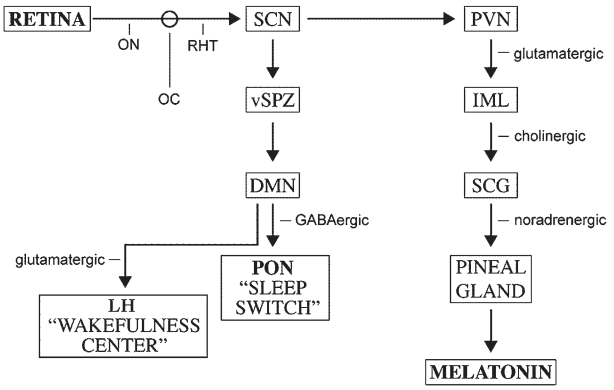

Figure 6. The RHT has the densest input to the SCN. The major neuronal pathway mediating the SCN-generated circadian rhythm of sleep and wakefulness is through a projection to the vSPZ, followed by second-order projection from the vSPZ to the DMN. The DMN sends primarily GABA projections to the PON (the "sleep switch") and glutamatergic projections to the LH (the "wakefulness center"). A subset of SCN neurons project directly to the dorsal parvocellular neurons in the autonomic subdivision of the PVN. The PVN sends glutamatergic projections to the sympathetic preganglionic neurons in the IML in the upper thoracic spinal cord. The IML sends cholinergic projections to the SCG. The SCG postganglionic sympathetic neurons send noradrenergic projections to the pineal gland, which activate α-and β-adrenergic receptors in the pineal, stimulating melatonin production (see Figure 8). DMN = dorsomedial nucleus; IML = intermediolateral cell column; LH = lateral hypothalamus; OC = optic chiasm; ON = optic nerve; PON = preoptic nuclei; PVN = paraventricular nucleus; RHT = retinohypothalamic tract; SCG = superior cervical ganglion; SCN = suprachiasmatic nucleus; vSPZ = ventral subparaventricular zone. See Figure 1 legend for expansion of other abbreviation.

disease and severe sundowning with 2 h/d of exposure to bright light between 7:00 PM and 9:00 PM for 1 week. Clinical ratings of sleep-wakefulness in the evenings improved in 8 of 10 patients. The authors concluded that "Evening bright light pulses may ameliorate sleep-wake cycle disturbances in some patients with Alzheimer's disease." In addition, Domzal et al[60] reported a majority of 30 stroke patients with circadian rhythm sleep disorder had "good results" with melatonin. Nevertheless, animal studies suggest melatonin may promote vasoconstriction, which could prove hazardous in patients with ischemic vascular disease.[61]

Narcotics, sedative-hypnotics, histamine-2 receptor blockers, antiparkinsonian medications, and anticholinergics should be avoided as all have been associated with delirium.[3] Psychoactive medications, such as thioridazine and haloperidol, frequently cause orthostasis and extrapyramidal side effects, whereas benzodiazepines often worsen agitation.[3] A multicenter, double-blind, placebo-controlled trial of atypical antipsychotics (risperidone, olanzapine, and quetiapine) was performed using 421 subjects with dementia, psychosis, aggression, or agitation.[62] No significant difference was found between drug and placebo, and there was a significant increase in adverse events with every atypical antipsychotic. Risperidone may

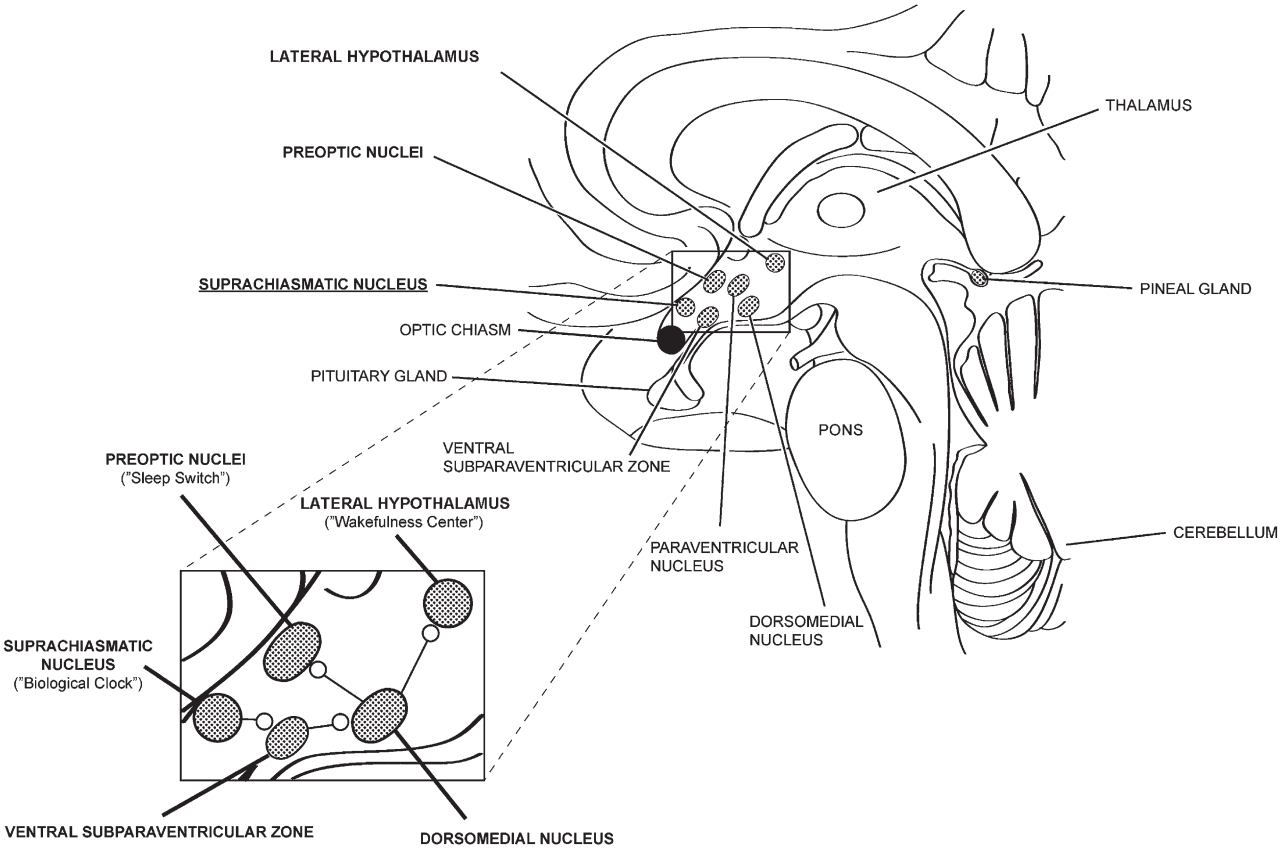

FIGURE 7. Diagrammatic representation of the brainstem in the parasagittal plane showing the close proximity of the SCN (the "biological clock") to the waking and sleep centers of the hypothalamus. The major neuronal pathway mediating the SCN-generated circadian rhythm of sleep and wakefulness is through a projection to the ventral subparaventricular zone (vSPZ), followed by second-order projection from the vSPZ to the dorsomedial nucleus (DMN). The DMN sends primarily GABA projections to the preoptic nuclei (the "sleep switch") and glutamatergic projections to the lateral hypothalamus (the "wakefulness center"). ○ = facilitatory. See Figure 1 and 6 legends for expansion of the other abbreviations.

also increase stroke in patients with dementia.[63] Shaw et al[64] have shown that agonists such as zolpidem and zaleplon that bind to the GABA A sleep-promoting receptors in the frontal cortex are more effective and produce fewer side effects in the treatment of sundowning than traditional hypnotics.

Initial therapy should always include the promotion of good sleep hygiene practices through cognitive behavioral therapy.[3,6] Good sleep hygiene is a positive set of habitual sleep-related behaviors that involve exercise, optimal diet (appropriate composition, size, and frequency of meals), regular sleep-wake schedules, and an ideal sleep environment (with proper dark-light contrast and temperature and noise levels). Good sleep hygiene uses a variety of cognitive behavioral therapeutic techniques (cognitive, sleep restriction, stimulus control, and relaxation therapies).[3] The literature supports using cognitive behavioral therapy in the treatment of insomnia in many geriatric populations and it is intuitive that optimizing sleep hygiene would be beneficial to patients with sleep problems and dementia.[2-6]

Neurodevelopmental Disabilities

Neurodevelopmental disabilities are a diverse group of chronic disorders that begin at any time during the development process (including conception, birth, and growth) up to 22 years and last throughout the patient's life.[65] Major disabilities include intellectual disability "mental retardation," learning disabilities, communication disorders, autism spectrum disorders, cerebral palsy, and neural tube defects. Among children with neurodevelopmental disabilities, the prevalence of sleep problems can be as high as 88%.[66] These patients' sleep problems are frequently chronic and are usually more difficult to treat than in their normally developing counterparts.[66] Early case reports showed melatonin corrected non-24-h sleep-wake cycles in blind, "retarded" (intellectually disabled) children.[67] In one study, to produce a desired phase advance of the circadian rhythm, melatonin (0.5 mg in aqueous solution containing 2% ethanol) was given 3 h before the expected endogenous secretion. Once phase advance was achieved, melatonin administration

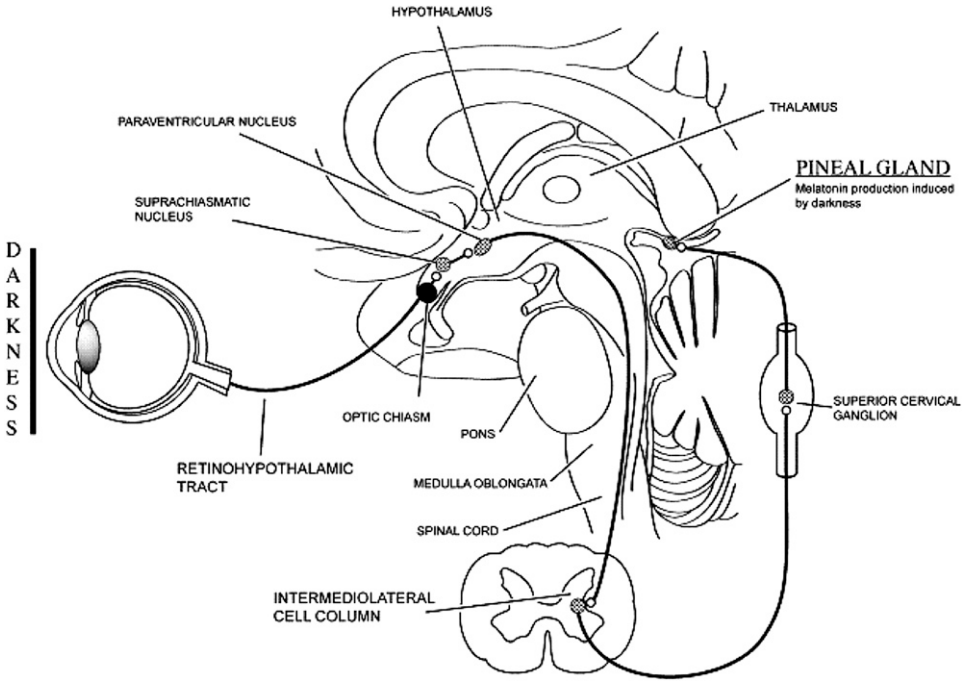

FIGURE 8. Daylight (bright light) is a powerful zeitgeber (external cue) that promotes wakefulness through the retinohypothalamic tract by activating a subset of SCN neurons, which subsequently inhibit sleep mechanisms of the paraventricular hypothalamic nucleus (PVH). Conversely, darkness (nighttime) disinhibits sympathetic fibers in the PVH, which stimulate neurons in the upper thoracic intermediolateral cell columns that subsequently excite neurons in the superior cervical ganglion, which project to the pineal gland and induce production of melatonin (a hormone that promotes sleep). ○ = facilitatory. See Figure 6 legend for expansion of the other abbreviations.

shortly before bedtime was sufficient to entrain the circadian rhythm on a stable 24-h cycle.[67] Positive parental comments have been obtained in a long-term follow-up of children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders who had participated in a placebo-controlled, double-blind, crossover trial of sustained-release melatonin, wherein there was a mean decrease in sleep latency of 30 min and increase of total sleep time by 30 min.[68,69] Several reviews of melatonin use in children with neurodevelopmental disabilities and sleep impairments conclude melatonin is beneficial and without significant adverse effects.[66]

Sleep-Related Movement Disorders

Restless Legs Syndrome and Periodic Limb Movements in Sleep

Restless legs syndrome (RLS) is a clinical diagnosis, whereas periodic limb movements during sleep (PLMS) require PSG documentation for accurate definition. RLS is clinically defined by the symptom acronym "URGE": Urge to move the limbs, worst at Rest, relieved by attempts to Go (move the limbs), and most disturbing in the Evening.[2] RLS can lead to insomnia, sleepiness, and problems with concentration, memory, motivation, anxiety, and depression. PLMS are found in up to 90% of patients with RLS. Walters and Rye[70] suggest that a general sympathetic hyperactivity intrinsic to RLS/PLMS may lead to hypertension and potentially stroke.

More than 50% of patients with idiopathic RLS have a family history of RLS, which generally segregates in an autosomal-dominant fashion with a penetrance rate of 90% to 100%.[71] Loci for RLS have been mapped on chromosomes 9p, 19p, 20p, 2q, 12q, and 14q.[71]

There is a probable contribution of a "spinal cord generator" to RLS.[71] Although functional MRI has shown an association between RLS sensory complaints and thalamic and cerebellar activation, a facilitation of the late component of the flexion reflex in RLS indicates there is a hyperexcitability of motor neurons, which may be exacerbated by a decrease in supraspinal inhibition.[71]

RLS/PLMS have been reported to follow stroke.[72] Specific structures in the lenticulostriate (basal ganglia) region might have a role in the pathophysiology of RLS/PLMS.[72] One group stated "A lesion in this area… may exert both an ascending disinhibition on sensorimotor cortex, and a disinhibition of descending inhibitory pathways, resulting in a facilitation of RLS and PLM."[72] This is consistent with evidence that

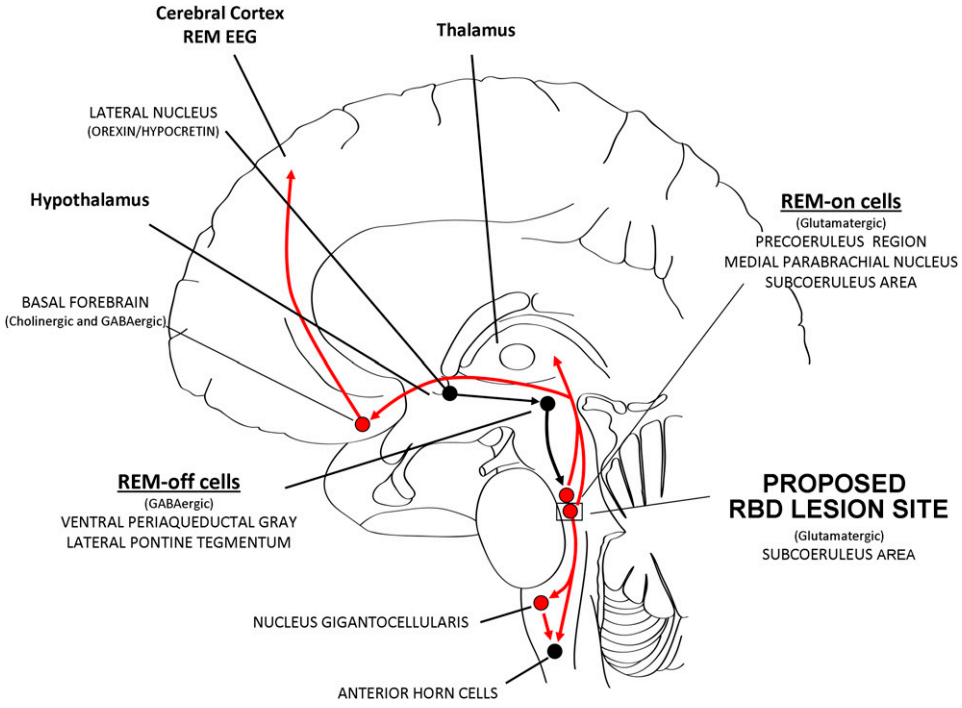

FIGURE 9. This parasagittal section of the brain and brainstem shows the suspected pathology explaining RBD, based upon the recently proposed "Flip-Flop" model of sleep state transitions by Saper et al.[7] In normal REM sleep, glutamatergic REM-on cells in what would be considered the subcoeruleus area (SCA) in cats and the sublaterodorsal nucleus in rats (an area presently not well defined in humans), directly and indirectly (through the nucleus gigantocellularis, one of the ventromedial groups of reticular nuclei in the medulla oblongata) cause hyperpolarization of anterior horn cells in the spinal cord, resulting in atonia. From animal studies, it has been hypothesized that in RBD, degeneration of the SCA disrupts descending tracts that would normally lead to atonia/paresis, thus allowing violent behaviors during REM (dreaming/paralyzed) sleep. Black circles and lines indicate nuclei and neuronal tracts normally inhibited during REM sleep; red circles and lines indicate nuclei and neuronal tracts normally activated during REM sleep; rectangle indicates proposed lesion site in RBD. RBD = rapid eye movement sleep behavior disorder. See Figure 1 legend for expansion of other abbreviations.

RLS/PLMS results from a CNS dopamine insufficiency/dysfunction (in the basal ganglia the ventral striatum receives its major dopaminergic innervation from the ventral tegmentum of the mesencephalon) and may explain successful post-stroke treatment of RLS/PLMS using dopamine agonists.[73]

Levodopa, when given with a dopa-decarboxylase inhibitor, has been associated with augmentation in 60% to 81% of patients, whereby the therapy itself contributes to an earlier onset of symptoms and overall worsening of RLS.[71] The use of the newer dopamine agonists with more direct effects on the D2 family of dopamine receptors of the basal ganglia may provide therapeutic efficacy with reduced augmentation.[71,74] The side effects of sleepiness, gambling, and increased sexual desires reported in Parkinson disease have been less of a problem in RLS, with no reports of "sudden onset of sleep" attacks.[71]

Iron is a cofactor in dopamine production, and iron deficiency is common in secondary forms of RLS such as iron-deficiency anemia, end-stage renal disease, and pregnancy.[2] If the serum ferritin is <45 to 50 μg/L, treatment should be considered using 325 mg of oral ferrous sulfate with vitamin C (100-200 mg) taken bid on an empty stomach, and a general workup should address the cause of iron deficiency.[2,71]

In idiopathic RLS, CSF ferritin reductions and elevated transferrin levels despite normal serum iron studies have suggested an iron deficiency of the CNS.[71,75] MRI and ultrasound studies of regional brain iron content and autopsies in patients with RLS have shown reduced iron in the substantia nigra and iron-related abnormalities.[71]

PARASOMNIAS

The REM Sleep Behavior Disorder

RBD is a parasomnia: an undesired physical phenomenon during sleep, associated with CNS activation primarily evidenced as increased skeletal muscle activity.[2] RBD occurs during REM sleep and is associated with violent dream (oneiric) behaviors, followed by arousals during which the patient describes dreams that parallel the observed behaviors (isomorphism).[76]

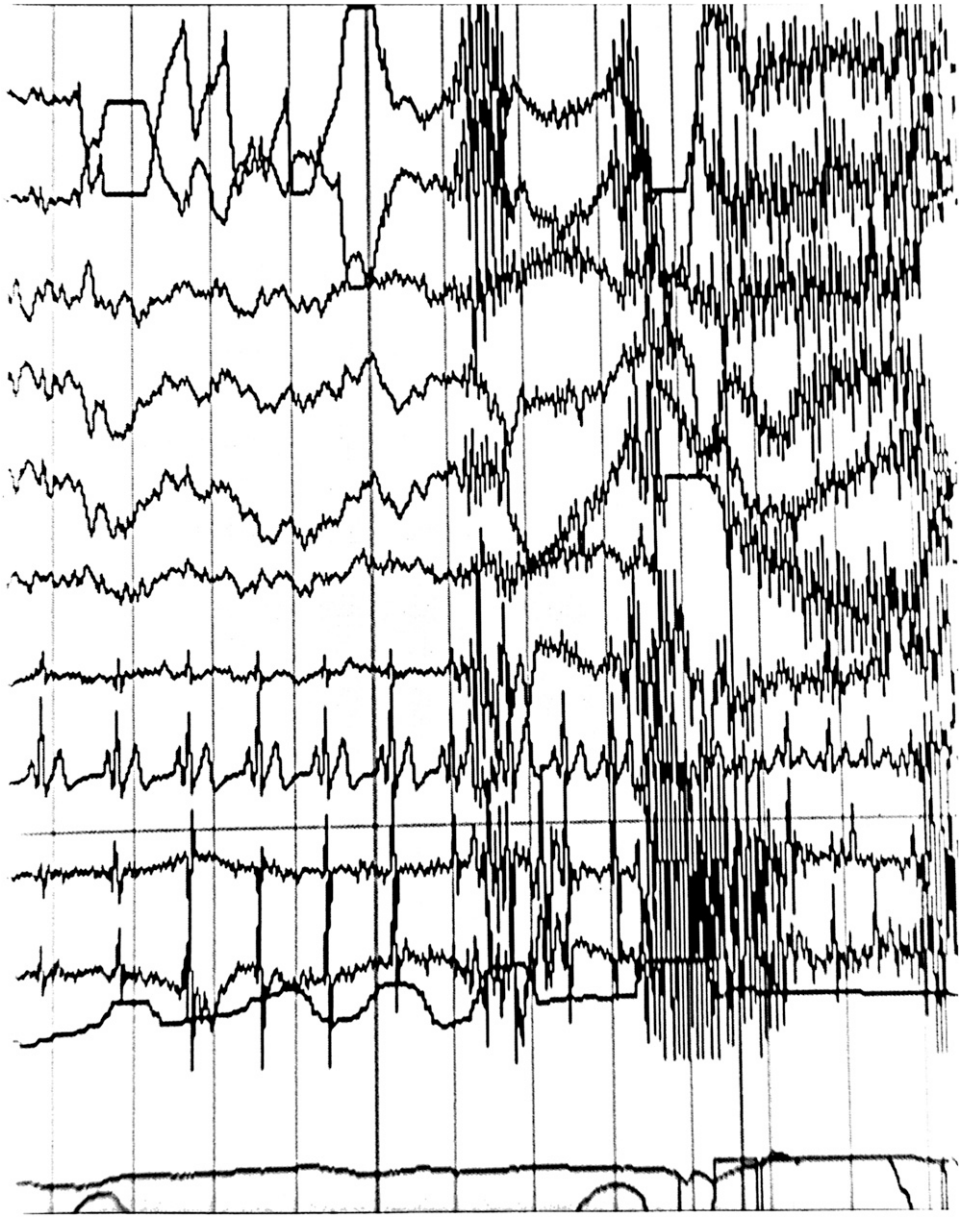

FIGURE 10. In a patient with suspected intractable sleep-related seizures, a polysomnogram tracing at the standard sleep recording speed of 10 mm/s showed an obstructive apnea immediately preceding his arousal and report of having "another seizure." Although the EEG appeared to show no clear epileptiform activity, it is contaminated by muscle/movement artifacts. (Adapted with permission from Dyken et al.[86])

Up to 77.1% of patients with RBD report dream-related injuries, which include subdural hemorrhage.[2,76] Normally during REM ("paralyzed" or "dreaming") sleep large movements do not occur because of uninhibited REM-on cells in the brainstem, from which caudally directed neuronal tracts lead to atonia by a hyperpolarized inhibition of anterior horn cells (Fig 9).[7] Diffusion-tensor imaging (a widely available MRI technique) and voxel-based morphometry (a measure of gray and white matter volume) in patients with idiopathic RBD has detected abnormalities in areas where REM sleep is modulated (the mesencephalic tegmentum, rostral pons, and pontine reticular formation).[77] A lesion affecting the brainstem structure in humans analogous to the sublaterodorsal nucleus in the rat and the subcoeruleus region in the cat has been proposed as the cause for RBD.[78]

RBD has been reported in a wide variety of neurologic disorders that might affect physiologic processes involving the brainstem, including multiple sclerosis, stroke, and CNS tumors, occurring in 47% of Parkinson disease patients with sleep complaints and in 69% of individuals with multiple systems atrophy.[2,76] In

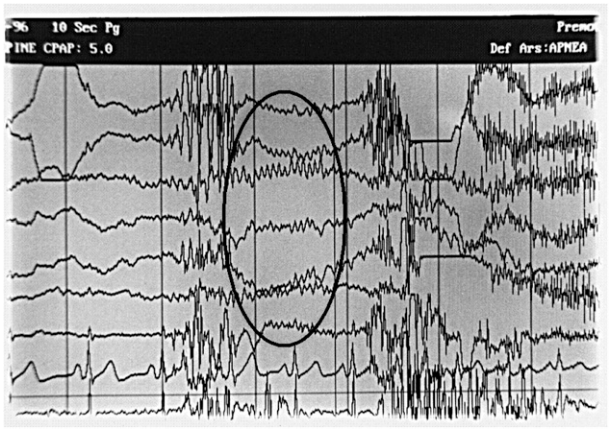

FIGURE 11. When the event in Figure 10 was reviewed using a sweep speed of 30 mm/s, it allowed for an expansion of the digital data analysis that revealed low-voltage β activity (enclosed within the oval) indicating the onset of an electrographic seizure. (Adapted with permission from Dyken et al.[86])

Schenck and Mahowald's[79,80] study of consecutively encountered subjects with RBD, 37.5% suffered RBD secondary to suspected CNS injury: 11 individuals had degenerative disorders (dementia, Parkinson disease, olivopontocerebellar degeneration, and Shy Drager syndrome), two suffered ischemic cerebrovascular disease, and single subjects had subarachnoid hemorrhage, brainstem astrocytoma, or multiple sclerosis.

RBD may be a risk factor for neurodegenerative disorders known as synucleinopathies (Parkinson disease, multiple systems atrophy, and Lewy body dementia).[81] In 2009, Postuma et al[82] quantified the risk of neurodegenerative disease in 93 patients diagnosed with idiopathic RBD. Of these individuals, 26 developed neurodegenerative disease: 14 with Parkinson disease, one with multiple systems atrophy, seven with Lewy body dementia, and four with Alzheimer disease. A life table survival curve was used to show the estimated 5-year risk for neurodegenerative disease of 17.7%, 10-year risk of 40.6%, and 12-year risk of 52.4%.

The ICSD-2 defines "subclinical RBD" when PSG reveals "REM without atonia" in the absence of violent dream report.[2] Subclinical RBD is frequent in neurodegenerative disorders and predicts future RBD in at least 25%.[2] Experts speculate if the degenerative process associated with synucleinopathies begins in the ventral mesopontine junction, RBD may precede the clinical diagnosis of a synucleinopathy by 10 years, whereas if the rostroventral midbrain is affected initially, then Parkinsonism will be the first indication of disease.[81] Although an autoimmune cause has been proposed for the synucleinopathies and RBD, studies to date have not been able to identify anti-locus coeruleus antibodies.[83]

The American Academy of Sleep Medicine's best practice guide for the treatment of RBD suggests the use of clonazepam or melatonin.[84] Clonazepam, successful in treating up to 90% of idiopathic RBD, has been used without significant tolerance or abuse and is recommended in RBD associated with neurodegenerative disorders.[2,79,80] Although the specific mechanism of action of clonazepam in RBD is not known, Mahowald and Schenck[79] have speculated that clonazepam may act preferentially through a serotonergic-like inhibition of motor excitatory systems. Doses from 0.5 mg to 1.0 mg usually reduce behaviors within a week.[79] When taken 2 h before bedtime, it may also address insomnia, RLS/PLMS, and reduce the risk of morning sedation. Caution is advised as it could exacerbate OSA or precipitate sundowning.[3,5] A safe sleeping environment is recommended; consider placing the mattress on the floor, removing dangerous objects, and securing the window area.[3,5,76]

In one study, to address cases in which clonazepam might be ineffective or cause undue side effects, a trial using 3 to 12 mg of melatonin every night at bedtime as a sole or addendum drug to clonazepam was

FIGURE 12. A 10-year-old girl with spells at night concerning for possible parasomnia (sleep terrors) had a prolonged evaluation in an epilepsy monitoring unit. Her assessment instead led to the diagnosis of nocturnal frontal lobe epilepsy. She had 40 stereotypical events captured with sleep video-EEG, only one of which showed rhythmic θ activity from the right frontal region (as shown by the arrows in the EEG channels enclosed by the boxes in the first picture frame) prior to a clinical seizure, which was characterized by a sudden frightened awakening and yelling for "Daddy" (see the second picture frame), and followed by crouching on bended hands and knees and subsequently clutching her father (see the third picture frame). (The patient provided written consent for the use of this photograph.) (Reprinted with permission from Dyken et al.[89])

performed on 14 patients with RBD.[85] Eight subjects had continued benefits from melatonin after 12 months of therapy, and side effects (which included morning headaches, morning sleepiness, and delusions/hallucinations) resolved with decreased dosage.

Sleep-Related Epilepsy

Nocturnal seizures can occur with elevated motor and autonomic activation, and as such the initial differential diagnosis can include "sundowning" and RBD.[3,76,86] Analysis of the stereotypic behaviors during continuous, prolonged video-EEG monitoring using an extended montage can confirm the diagnosis.

Patients with cortical lesions from stroke, tumors, trauma, and dementia are prone to seizures. Epileptiform activity associated with generalized seizures tends to increase in non-REM (N) sleep, whereas partial seizures are particularly activated by stages N1 and N2 sleep.[86,87] A firm diagnosis is afforded when ictal/interictal epileptiform discharges are captured immediately before, during, or after a clinical spell. During a seizure, the EEG classically shows generalized depression or slowing, rhythmic slow wave or spike/poly-spike and wave activity immediately prior to or during a clinical event, with postictal slowing or depression following a spell.

Nevertheless, when attempting to differentiate a nocturnal seizure from a parasomnia, there are significant confounding issues associated with the diagnostic accuracy of PSG that Dyken et al[86] have referred to as the "interference pattern." The standard PSG recording speed of 10 mm/s has a compressing effect that can obscure subtle epileptiform activity in underlying electromyographic movement artifact (Figs 10, 11). In addition, the standard PSG recording uses a minimal array of monitoring electrodes that might not cover the brain area of epileptiform discharge. Tao and colleagues[88] estimate at least 10 to 20 cm^2 of synchronously activated gyral cortex is needed to detect spike activity (seizure potential) using scalp EEG electrodes. This has been used by some experts to explain why deep-seated frontal lobe seizure foci do not routinely produce an EEG abnormality, especially with the limited analysis provided by routine PSG. As such, we routinely consider a 1- to 3-day continuous assessment of the patient during a flurry of activity in our epilepsy monitoring unit using an extended EEG montage (Fig 12).[89]

Summary

There is a strong association between neurologic diseases and sleep problems, especially when there is injury to central sleep-wake mechanisms. A fundamental knowledge concerning the basic anatomy and physiology of these mechanisms provides a rationale for pharmacologic interventions. Nevertheless, nonpharmacologic treatments are important as these patients are often prone to the adverse effects of many routinely prescribed medications. Nonpharmacologic treatments include the use of CPAP and NPPV for sleep-related breathing disorders and bright light therapy for circadian rhythm sleep disorders. Although the treatments presented in this manuscript have largely focused on primarily addressing specific sleep-related complaints, every therapeutic regimen should include good sleep hygiene practices that use cognitive behavioral therapy.

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