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# Sleep Disorders in Neurologic Practice

## A Case-based Approach



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### KEYWORDS

- Sleep disorders • Narcolepsy • Restless leg syndrome • Sleep apnea
- REM sleep behavior disorder • Insomnia • Circadian rhythm disorders

### KEY POINTS

- Patients with neurologic conditions are at increased risk for comorbid sleep disorders, including insomnia, sleep disordered breathing or sleep apnea, circadian rhythm disorder, restless legs syndrome, rapid eye movement–sleep behavior disorder, and narcolepsy.
- Identification and treatment of sleep disorders may improve control of the underlying neurologic condition as well as improve quality of life, and thus comprises a critical component of patient care.
- A reciprocal relationship may exist whereby a sleep disorder can exacerbate a neurologic condition, and the neurologic condition or its treatments can increase risk of a sleep disorder.

### CASE A: EPILEPSY AND SLEEP DISORDERED BREATHING

Patients with epilepsy can experience a variety of sleep-related symptoms that may increase the frequency of seizures.

#### *Case Presentation*

A 43-year-old woman with a history of epilepsy since childhood presented to neurology clinic for a follow-up visit. She had complex partial seizures with occasional secondary generalization that developed after a bout of meningitis at 8 months of age. She was previously treated with phenobarbital and phenytoin for many years and was later transitioned to carbamazepine monotherapy approximately 10 years ago.

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Lamotrigine was subsequently added 8 years ago because of poor seizure control. She currently reported approximately 8 to 9 breakthrough seizures per year.

Her chief complaint at the follow-up visit was gradually worsening daytime sleepiness and inadvertent dozing when she was sedentary. On further questioning, she endorsed mild snoring on most nights, restless and poor quality sleep, difficulty falling asleep several times per week, and frequent nighttime awakenings. She had no bed partner but did not think she had any seizures during sleep. Her Epworth Sleepiness Scale (ESS) score was 14 out of 24, indicating excessive sleepiness (normal is <10; [Table 1](#)). On examination, she had normal waking oxygen saturation, an increased body mass index (BMI) of 31 kg/m<sup>2</sup>, neck circumference of 42 cm (16.5 inches), and narrow upper airway anatomy with a modified Mallampati III airway ([Fig. 1](#)), low-lying soft palate, an elongated uvula, and macroglossia. Her neurologic examination was unremarkable.

### Clinical Questions

1. What are some common causes of excessive daytime sleepiness in individuals with epilepsy?
2. What are likely mechanisms by which sleep disturbances may worsen seizures/increase seizure frequency in patients with epilepsy?
3. In contrast, what mechanisms may confer an increased risk of sleep disordered breathing among patients with epilepsy?

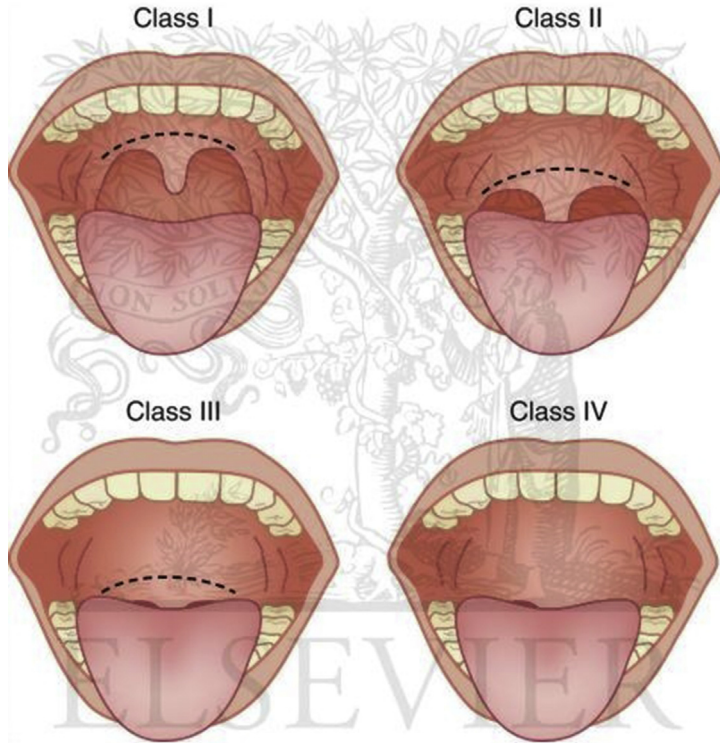
### Discussion

Hypersomnolence, a state of recurrent episodes of excessive daytime sleepiness, is frequently encountered among patients with epilepsy and is usually secondary to underlying causes.<sup>1</sup> These causes can include a comorbid sleep disorder such as obstructive sleep apnea (OSA) or insomnia, medication-related adverse effects, psychiatric comorbidities such as depression, or behavioral patterns that may disrupt sleep, such as poor sleep hygiene. Recent data examining sleep in individuals with epilepsy show evidence of fragmented sleep architecture on

<b>Situations</b>	<b>Chance of Dozing</b>
Sitting and reading	0, 1, 2, 3
Watching television	0, 1, 2, 3
Sitting inactive in a public place (eg, in a theater or a meeting)	0, 1, 2, 3
As a passenger in a car for an hour without a break	0, 1, 2, 3
Lying down to rest in the afternoon when circumstances permit	0, 1, 2, 3
Sitting and talking to someone	0, 1, 2, 3
Sitting quietly after a lunch without alcohol	0, 1, 2, 3
In a car, while stopped for a few minutes in traffic	0, 1, 2, 3

The ESS was developed by researchers in Australia and is widely used by sleep professionals to appraise the degree of excessive sleepiness. Patients are asked “How likely are you to doze off or fall asleep in the following situations, in contrast with feeling just tired?” “This refers to your usual way of life in recent times.” Patients are instructed to use the scale to rate the level of their sleepiness in each of the following situations/scenarios: 0, no chance of dozing; 1, slight chance of dozing; 2, moderate chance of dozing; 3, high chance of dozing.

*Modified from* Johns M. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–45.



**Fig. 1.** The Mallampati Airway Classification. During the Mallampati assessment, the patient is instructed to open his or her mouth as wide as possible, while protruding the tongue as far as possible. Patients are instructed to not emit sounds during the assessment. Class I: good visibility of the soft palate and entire uvula; Class II: partial visualization of the soft palate and portion of uvula; Class III: soft palate visible only (may include base of uvula), and; Class IV: soft palate not visible. The system is often used to judge the likelihood of sleep disordered breathing, and may be helpful especially in patients who have class III and IV airway.

electroencephalogram (EEG) with increased spontaneous arousals and awakenings.<sup>2</sup> However, fragmented sleep by electrographic recording does not necessarily correlate with daytime symptoms. Simply having epilepsy is similarly not an independent risk factor for hypersomnia, as shown by comparable scores on objective and subjective measures of sleepiness in untreated patients with epilepsy and healthy controls.<sup>1,3</sup>

In the case described earlier, the patient has features that are suggestive of OSA. The differential diagnosis also includes nocturnal seizures and insomnia. As a premenopausal woman, she does not conform to the demographic profile of a typical patients with OSA given that OSA more commonly occurs in older patient cohorts and in men.<sup>4</sup> Her risk factors for OSA include snoring; obesity; having narrow upper airway anatomy, which predisposes her to upper airway collapse; and having a history of epilepsy.

Epilepsy is independently associated with an increased risk of OSA. Both polysomnography-based and questionnaire-based studies have shown a higher prevalence of OSA among individuals with epilepsy.<sup>5-8</sup> There is evidence that even patients with well-controlled epilepsy have higher OSA rates of between 15% and 30% in

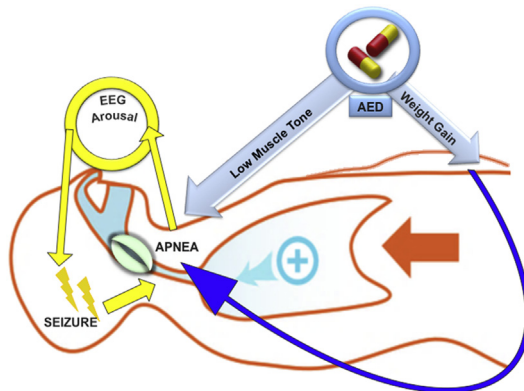
polysomnography-based studies, compared with general population estimates of 2% in women and 4% in men.<sup>5,6,9</sup>

Comorbid OSA can have important implications for seizure control as well as quality of life (QOL), cardiovascular risk, and fatigue symptoms. Untreated OSA can worsen seizure control in patients with epilepsy and may provoke spike-wave discharges during sleep.<sup>10,11</sup> Appropriate use of continuous positive airway pressure (CPAP) often improves seizure control and reduces occurrence of interictal discharges, even in medically refractory epilepsy.<sup>5,12</sup>

The mechanism by which epilepsy is associated with OSA has not been clearly elucidated, but studies point to a reciprocal relationship (Fig. 2). OSA can worsen seizure control by increasing sympathetic nervous system activity and overall neuronal excitability.<sup>7,13</sup> OSA also causes frequent sleep-wake transitions and sleep fragmentation, which can trigger seizures.<sup>11</sup>

Potential ways that epilepsy can cause sleep apnea include neuronal abnormalities that adversely affect central nervous system (CNS) control of respiration and upper airway tone, weight gain caused by antiepileptic drugs (AEDs) and a less active lifestyle, and AED direct effects on reduction of upper airway muscle tone.<sup>6</sup> There are also some data to suggest that seizures can directly cause apneas, possibly via seizure-induced reduction of upper airway muscle tone and respiratory control. Seizures involving the amygdala are shown to episodically suppress respiration, and therefore could contribute to both sleep apnea and to sudden unexpected death in epilepsy.<sup>14</sup> In support of this hypothesis, a case report showed resolution of sleep apnea after epilepsy surgery in a nonobese 18-year-old man, despite no change in AEDs and a slight postoperative weight gain.<sup>15</sup>

Epilepsy can also lead to daytime hypersomnia for reasons other than sleep disordered breathing. Seizures, sometimes occurring undetected while asleep, may cause postictal somnolence the next day.<sup>16</sup> Moreover, AEDs can disturb sleep architecture and contribute to hypersomnia or insomnia with ensuing daytime sleepiness. AEDs with detrimental sleep effects include phenobarbital, phenytoin, valproic acid, and



**Fig. 2.** Epilepsy and obstructive sleep apnea (OSA). Case A: reciprocal relationship between epilepsy and sleep apnea. Antiepileptic drugs (AEDs) can indirectly increase risk of sleep apnea by contributing to weight gain and causing reduced upper airway muscle tone. Furthermore, seizures during sleep can directly induce apneas. Sleep apnea causes frequent electroencephalogram (EEG) microarousals out of sleep, and over the long term can increase overall sympathetic nervous system activity; this can subsequently increase seizure frequency in individuals with epilepsy.

high-dose levetiracetam.<sup>17</sup> However, some AEDs have no effect or can improve sleep architecture, possibly by reducing interictal discharges or subclinical nocturnal seizures.<sup>18,19</sup>

### **Summary of Case Presentation**

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In this case, the patient underwent polysomnography testing, which showed moderate to severe OSA with associated episodic moderate oxygen desaturations to a nadir of 81%, from a normal baseline level of 96%. There were no significant interictal discharges or electrographic seizures during sleep during the study. She subsequently initiated treatment with CPAP during sleep. After an initial period of acclimation to CPAP use, at her next follow-up she reported considerable improvement in daytime sleepiness with an improved ESS score of 6 out of 24 and a reduction in nighttime awakenings. She had had no seizures since starting CPAP 3 months prior, and she was optimistic about eventually attempting to wean off 1 of her AEDs.

## **CASE B: MULTIPLE SCLEROSIS AND INSOMNIA**

Sleep disturbance is a frequent complaint among individuals with multiple sclerosis (MS), often leading to worse QOL compared with patients without sleep disturbances.

### **Case Presentation**

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A 32-year-old woman with relapsing-remitting MS presented for neurologic follow-up with a chief complaint of severe fatigue during the day and poor sleep at night. She was diagnosed with MS 5 years previously and had been treated since that time with interferon beta-1b. She had had 2 relapses since her initial diagnosis, most recently 18 months ago, with mild residual disability. Recent brain MRI showed several periventricular demyelinating plaques, as well as a small plaque in the spinal cord at C4. Current examination findings included normal vital signs, BMI of 23 kg/m<sup>2</sup>, slightly reduced visual acuity of 20/40 on the left, left-sided numbness, mild distal right upper extremity weakness with 4/5 grip strength and mild right lower extremity weakness with 4+/5 strength in the iliopsoas and quadriceps muscles. She also had symptoms of urinary urgency and nocturia with occasional urinary incontinence. She complained of frequent bilateral leg spasms, worse on the right, which were triggered by walking or stretching her limbs. She had trouble falling asleep because of ruminative thoughts and anxiety, and limb discomfort also made it difficult for her to physically relax in bed. She estimated that it took her approximately 2 hours to fall asleep on most nights. She found herself awakening multiple times nightly because of spasms or nocturia, and then had trouble quieting her thoughts in order to go back to sleep. She denied snoring or breathing pauses in sleep. She indicated episodes of irresistible and unintentional sleep attacks during the day. She was distressed by her insomnia, which she thought was contributing to feeling depressed and irritable and causing poor memory and fatigue during the day.

### **Clinical Questions**

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1. How common is insomnia in individuals with MS?
2. Does MS cause insomnia?
3. What treatment approaches for insomnia are effective in MS?

### **Discussion**

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MS is a chronic condition with associated medical and psychiatric comorbidities that can contribute to a reduced health-related QOL. Prominent among these are sleep

disturbances. Chronic insomnia is highly prevalent in MS with reported rates of 22% to 52%.<sup>20,21</sup> Chronic insomnia is defined as at least 3 months of difficulty initiating and/or maintaining sleep, with ensuing impairments in daytime functioning at least 3 times per week.<sup>22</sup> Among patients with MS, insomnia is more prevalent in women, individuals with mood symptoms, and those with multiple medical problems.<sup>20</sup> Insomnia is also associated with poor QOL, highlighting the importance of identifying, evaluating, and treating this common condition.<sup>23</sup>

Insomnia in MS is frequently not intrinsic, but occurs secondary to medical symptoms such as pain, spasticity, and nocturia, and psychiatric disorders such as depression and anxiety.<sup>24</sup> **Fig. 3** Pain and discomfort from spasticity and mobility limitations can contribute to sleep-onset and sleep-maintenance insomnia and daytime fatigue.<sup>25,26</sup> Although not specific for MS, chronic pain conditions can adversely affect sleep EEG architecture by causing alpha intrusions during deep slow wave sleep, more frequent arousals into lighter sleep stages, and reduced sleep efficiency.<sup>27</sup> A reciprocal relationship exists between pain and sleep by which poor or fragmented sleep can also worsen the perception of pain, thereby perpetuating the maladaptive cycle.<sup>28</sup> Nocturia and other symptoms of neurogenic bladder can contribute especially to sleep-maintenance insomnia, with frequent nocturnal awakenings and ensuing difficulty falling back to sleep. Pharmacologic treatment of the underlying bladder dysfunction can help to improve sleep consolidation and reduce daytime fatigue.<sup>29</sup>

Mood disorders also play a prominent role. Patients with MS with depression are much more likely to have insomnia compared with the overall MS population.<sup>30</sup> Effectively treating depression and anxiety with psychotherapy directly correlates with the degree of insomnia improvement, particularly in sleep-onset insomnia.<sup>30</sup> Pharmacologic treatment with antidepressant medication should also be considered as part of a comprehensive approach to managing depression and fatigue symptoms in MS. For example, studies have found that use of duloxetine, a dual serotonin and norepinephrine reuptake inhibitor, was associated with improved mood, lessened fatigue, reduced pain, and improved sleep quality.<sup>31,32</sup>



**Fig. 3.** Multiple sclerosis (MS) and insomnia. Multiple medical and psychiatric comorbidities can interact to contribute to secondary insomnia in individuals with multiple sclerosis.

As in the general population, primary psychophysiological insomnia can also occur in patients with MS. This phenotype of insomnia is characterized by a learned pattern of maladaptive behaviors and negative associations with regard to sleep, and psychological and physiologic heightened arousal during sleep attempts.<sup>33</sup> An effective nonpharmacologic treatment is a course of cognitive behavior therapy for insomnia (CBTi) that targets both excessive thoughts about sleep inability and negative behaviors that maintain the dysfunctional sleep habits.<sup>34,35</sup>

Medications for sleep can also be used, particularly when treatment of underlying medical and psychological problems have not resulted in a significant improvement in insomnia. However, data regarding their efficacy in MS are sparse and the available studies have yielded mixed results; for example, with eszopiclone causing improved total sleep time but insufficient symptomatic improvement in fatigue.<sup>36</sup> Hypnotic medications for the general population consist of benzodiazepine receptor agonists that act on the gamma-aminobutyric acid A receptor complex, as well as newer generation nonbenzodiazepine receptor agonists with shorter half-lives and fewer side effects, including zolpidem (regular and controlled release), zaleplon, and eszopiclone.<sup>37</sup> Melatonin receptor agonists (ramelteon) may be helpful in patients with sleep-onset insomnia. Doxepin, a histamine H<sub>1</sub> receptor antagonist, has also received US Food and Drug Administration (FDA) approval for the treatment of chronic sleep initiation and maintenance insomnia. The most recently approved hypnotic agent is suvorexant, a hypocretin receptor antagonist, currently available for management of sleep-onset and maintenance insomnia.<sup>38,39</sup>

Other sleep disorders can also co-occur with MS, including (in non-population-based samples) narcolepsy (prevalence of 0%–1.6%), restless legs syndrome (RLS; prevalence of 14%–58%), rapid eye movement (REM) sleep behavior disorder (RBD; prevalence of 2%–3%), and OSA (prevalence of 7%–58%).<sup>40</sup> Although sleep symptoms are present in most patients with MS, often the conditions are not formally diagnosed or sufficiently evaluated by providers.<sup>41,42</sup> Varied rates of awareness and testing by clinical providers may in part explain the wide range of reported prevalences for sleep disorders in MS.

### **Summary of Case Presentation**

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In the case discussed earlier, the patient's symptoms of pain, depression, and anxiety were targeted as the first steps in improving sleep. She was started on baclofen for treatment of painful limb spasms and referred to a psychologist for CBTi as well as for fatigue and mood management. At her 6-week follow-up visit, she reported partial improvement in her sleep symptoms. She was able to fall asleep within 30 minutes on most nights, and was less prone to excessively ruminating and worrying about sleep. Spasms were improved with baclofen, which she used primarily in the evenings because it also made her drowsy. She continued to have nocturia 3 to 4 times per night and therefore was given a prescription for oxybutynin, which significantly improved the frequency of nocturia and sleep continuity on subsequent visits.

### **CASE C: ALZHEIMER DISEASE AND CIRCADIAN RHYTHM DISORDER, ADVANCED SLEEP PHASE TYPE**

Sleep disturbances can pose a significant challenge in the management and QOL of patients with dementia. Interventions to improve sleep in this population are important because they can improve nighttime sleep and daytime wakefulness, and reduce caregiver burden.



### **Case Presentation**

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An 83-year-old man presents to neurology clinic for initial consultation regarding memory loss. He lives with his daughter, who accompanied him to the appointment. They describe a 5-year history of insidious and slowly progressive memory loss with symptoms of forgetfulness, inability to manage complex tasks such as his finances, confusion when trying to follow directions, and frequent repetitive questioning. He had to stop driving because of several instances of getting lost in familiar areas. A prior neuropsychological testing battery had revealed primarily amnesic mild-to-moderate cognitive impairment with a lesser degree of executive dysfunction, in a pattern most consistent with a neurodegenerative process such as Alzheimer disease (AD). On neurologic examination, his Mini-Mental State Examination score was 23 out of 30 (reflecting mild cognitive impairment) and he had an otherwise unremarkable neurologic examination with no extraocular movement abnormalities, no tremor or motor findings, and intact gait and balance. Brain MRI showed moderate diffuse cerebral atrophy and mild periventricular leukoaraiosis.

His daughter inquired about the possibility of treatment with a cholinesterase inhibitor and whether her father could be prescribed a sleeping medication to help address his early morning awakenings. Further questioning of his sleep pattern indicated that he would doze off intermittently throughout the afternoon and evening in his recliner, but seemed to have significant difficulties maintaining sleeping during the later part of the night and would often be heard pacing around the house after 4 AM. His daughter was very concerned about the risk of falls or accidents as a result of the patient's pre-dawn restlessness.

### **Clinical Questions**

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1. What are likely mechanisms for the development of sleep cycle alterations and daytime sleepiness in individuals with AD?
2. What are some potential sequelae and adverse health effects of untreated circadian rhythm disorders among elderly individuals or patients with dementia?

### **Discussion**

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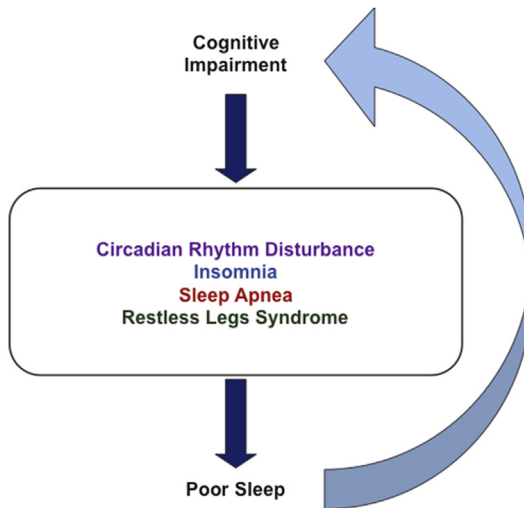
Changes in sleep patterns and sleep stage architecture can occur with advancing age. Normal age-related changes after age 60 years can include fragmentation of sleep with frequent brief EEG arousals, decreased sleep efficiency (time spent asleep compared with time spent attempting to sleep), increased time to onset of sleep, and a reduction in the proportion and EEG spectral power of slow wave and REM sleep.<sup>43–45</sup> These disturbances in sleep become even more pronounced among individuals with dementia syndromes such as AD.<sup>46</sup>

Older individuals and particularly those with cognitive impairment are much more likely to experience decreased total sleep time at night, early morning awakenings, and a propensity to nap throughout the day. This alteration in circadian rhythmicity of sleep with a propensity for phase advancement of sleep timing is known as advanced sleep phase syndrome (ASPS).<sup>43,47</sup> Circadian rhythms are generated by biological clocks that use external cues such as light to entrain and coordinate biological processes. Circadian control of sleep-wake cycles is mediated by the suprachiasmatic nucleus (SCN) of the hypothalamus using the pineal gland-produced hormone melatonin.<sup>48</sup> In AD, neurodegeneration of cortical and subcortical areas, including neuronal loss in the SCN, may be responsible for circadian abnormalities such as ASPS as well as the phenomenon of worsened evening confusion and behavioral problems known as sundowning.<sup>43,48</sup>

Patients with AD frequently develop irregular sleep rhythms with difficulty staying asleep for consolidated periods of time, long awakenings at night, and daytime sleepiness requiring frequent naps. These disrupted sleep behaviors can be problematic both for patients and for their caregivers. Patients with AD who are active late at night are at higher risk for falls, accidents, wandering, or confusion. Sleepiness during the day also interferes with caregiving and medication schedules as well as reducing the opportunity for exercise and social interaction. In addition, daytime sleepiness and fragmented or inadequate nighttime sleep can contribute to poor cognitive performance both in patients with AD and in healthy adults because of adverse effects on attention, concentration, and sustained vigilance.<sup>49</sup>

In addition to circadian rhythm disturbance, other sleep disorders can also be associated with AD. There is an increased risk of OSA; CPAP treatment can often improve cognition in individuals with dementia and comorbid OSA.<sup>35</sup> Other comorbid sleep disorders include insomnia, which is usually secondary to factors such as ASPS, pain, nocturia, RLS, or periodic limb movement disorder of sleep (PLMDS).<sup>50</sup> In elderly or institutionalized adults, the increased risk for RLS and PLMD may be associated with reduced iron stores or use of neuroleptic medications, including selective serotonin reuptake inhibitors.<sup>50</sup> RLS and PLMD may contribute to poor sleep, and may be difficult to diagnose in cognitively impaired individuals who cannot provide a reliable history. Poor sleep may also exacerbate the symptoms of many comorbid sleep disorders, including RLS, PLMD, and ASPS<sup>49</sup> (Fig. 4).

Several recent studies have found an association between early markers of sleep and circadian disruption and subsequent onset of cognitive impairment, as shown in Fig. 4.<sup>51–53</sup> It is possible that sleep architecture changes and circadian abnormalities play a causal role in contributing to the development of dementia in healthy older individuals.<sup>54</sup> Studies in animal models have investigated possible mechanisms for



**Fig. 4.** Alzheimer and ASPS. A prominent bidirectional relationship exists between cognitive impairment and poor sleep. Sleep loss can transiently reduce attention and concentration, and may play a direct role in the development of neurodegenerative disorders such as Alzheimer disease. Individuals with dementia, including Alzheimer disease, are at higher risk for sleep disorders such as circadian rhythm disturbance, insomnia, sleep apnea, and RLS/periodic limb movement disorder, all of which can reduce sleep quality and duration.

this and found evidence that amyloid- $\beta$  accumulation in the brain is under circadian control.<sup>55</sup> Moreover, sleep loss in both animals and humans is associated with increased levels of amyloid- $\beta$ , which is thought to be the inciting event in the development of AD.<sup>56–58</sup>

Given the prominent bidirectional relationship between sleep regulation and cognitive function, sleep should be an important concern in the management of AD. Circadian rhythm disturbance and ASPS can be treated primarily with behavioral interventions. These interventions include optimizing the patient's environment to ensure adequate natural light exposure and exercise during the day, minimizing prolonged naps and sedentary status during the day, avoiding excessive light exposure and mental or physical stimulation in the evenings, and adjusting the timing of medication administration to facilitate sleep at night when possible.<sup>43</sup> For patients with AD without ASPS, bright light therapy with at least a 30-minute exposure to full-spectrum light using a light box or natural sunlight in the mornings is effective. For patients with ASPS, bright light exposure is helpful during periods of excessive sleepiness in the late afternoon to early evening, because it may help delay the circadian phase in ASPS.<sup>59</sup> Pharmacologic therapies may also have some benefit. Treatment of insomnia with the dietary supplement, melatonin, is frequently used in the evenings for circadian regulation, but some studies have shown no significant benefit in patients with AD.<sup>50,60</sup> Other pharmacologic approaches have been tried with varying degrees of success, including 1 trial of trazodone that showed significant improvement in sleep among patients with AD.<sup>61</sup> Pharmacologic treatments for sleep should be used judiciously in AD with careful consideration of the potential benefit versus the inherent risks and side effect profiles.<sup>50</sup>

### **Summary of Case Presentation**

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In the case of the patient with AD, he was diagnosed with ASPS. Behavioral changes focused on activities conducive to improving the circadian desynchronization (ie, a loss of synchrony of the sleep-wake cycle) were initially recommended as a first-line treatment. At the subsequent follow-up visit, his daughter reported mild improvements in nighttime sleep after the patient joined an adult day program to increase his daytime activity and decrease likelihood of napping. He was also taking short walks with his daughter in the late afternoon for increased light exposure. As a safety measure, he was now sleeping downstairs and with a night-light to reduce fall risk in case of nocturnal awakenings. He was advised to take his donepezil dose in the mornings rather than at bedtime to reduce the potential alerting effects of acetylcholinesterase inhibitors.

### **CASE D: SECONDARY NARCOLEPSY IN A PATIENT WITH NEUROSARCOIDOSIS OF THE HYPOTHALAMUS**

Narcolepsy type 1 (NT1; formerly narcolepsy with cataplexy) is a category of CNS hypersomnia reflecting a dysfunction of the hypocretin-producing neurons in the diencephalon. Most patients with NT1 and cataplexy have low or undetectable levels of hypocretin-1 in the cerebrospinal fluid (CSF). Pathologically low hypocretin levels have been reported in patients with underlying diencephalic injuries caused by CNS disorders, including stroke, tumors, neurosarcoidosis, or demyelinating disease.

### **Case Presentation**

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A 53-year-old man, who was previously in good health, presented from an outside institution for a higher level of care with alterations in consciousness, with unexplained weight loss, fevers, night sweats, and severe pathologic hypersomnolence.<sup>62</sup> Brain MRI

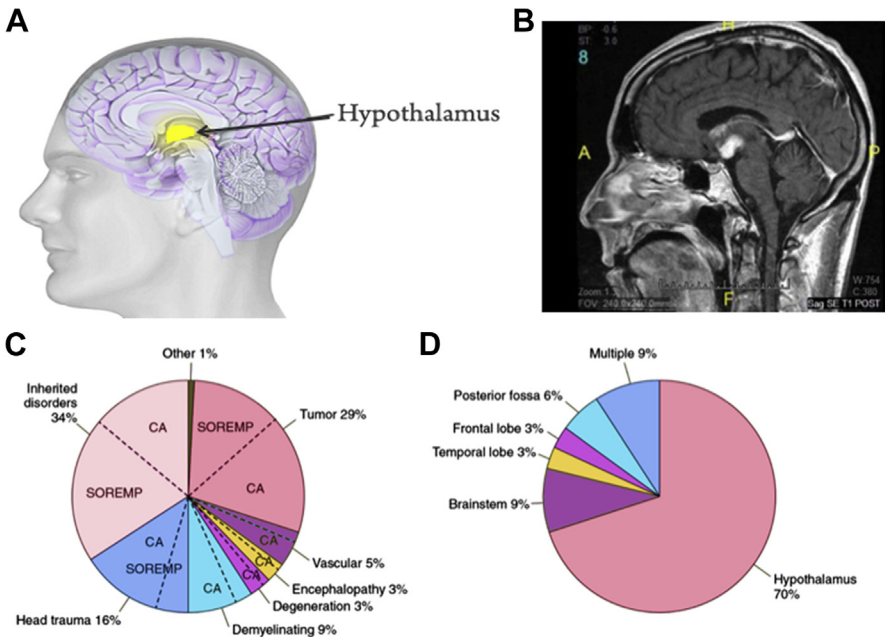
revealed a diencephalic lesion with specific involvement of the hypothalamus demarcated with both T2 and T1 postcontrast hyperintensity (**Fig. 5**) within this region.

Hypothalamic biopsy showed neurosarcoidosis exemplified by noncaseating granulomas and exclusion of other infectious diseases. Physical examination revealed a lethargic, thin man who aroused sporadically to verbal stimuli, and showed a brief attention span of approximately 10 seconds, lapsing back to sleep.<sup>62</sup>

The patient proceeded to undergo a lumbar puncture revealing a CSF hypocretin level of 0 pg/mL. The CSF was otherwise clear and colorless with 2 red blood cells, 3 white blood cells, without evidence for demyelination. Major histocompatibility complex, class II, DQ beta 1 0602 (human leukocyte antigen [HLA]-DQB1\*0602) was negative.<sup>62</sup>

### Clinical Questions

1. What is the most likely explanation for the patient's severe hypersomnolence?
2. What are the different types of hypersomnias related to a CNS cause?



**Fig. 5.** Secondary narcolepsy caused by diencephalic injury. (A) The location of the diencephalon, where the wake-stabilizing hypocretin-producing cells are localized. (B) Brain MRI indicated involvement of the hypothalamus, showing postcontrast hyperintensity within the anterior hypothalamus. The patient did not experience any brainstem involvement, nor were any appreciable lesions found in the locus coeruleus or raphe nuclei. (C, D) Neurologic diseases and location of brain lesions in 113 cases of secondary narcolepsy. (C) Neurologic diseases are shown by category reported as secondary narcolepsy. Reported here are tumors, inherited disorders, and head trauma, which are the 3 most frequent causes. The percentage of cataplexy (CA) or sleep-onset REM periods (SOREMP) is denoted in each category with a dashed line. (D) Location of brain lesions in symptomatic patients with narcolepsy associated with brain tumor; the hypothalamus and adjacent structures are the most common location. Included are 113 symptomatic cases of narcolepsy. (Modified from Kanbayashi T, Sagawa T, Takemura F, et al. The pathophysiologic basis of secondary narcolepsy and hypersomnia. *Curr Neurol Neurosci Rep* 2011;11(2):235–41.)

3. What is the differential diagnosis of narcolepsy?
4. What are specific drug treatments for centrally mediated hypersomnia?

### Discussion

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The International Classification of Sleep Disorders-III (ICSD-III) divides narcolepsy into 2 subtypes: narcolepsy type 1 (NT1; with cataplexy, or associated with low hypocretin levels), and narcolepsy type 2 (NT2; without cataplexy, and with normal hypocretin levels).<sup>63</sup> Secondary narcolepsy caused by a known underlying CNS disorder, as in the case presented earlier, is referred to as NT1 caused by a medical condition (when hypocretin levels are low) or NT2 caused by a medical condition (when hypocretin levels are normal).<sup>63</sup>

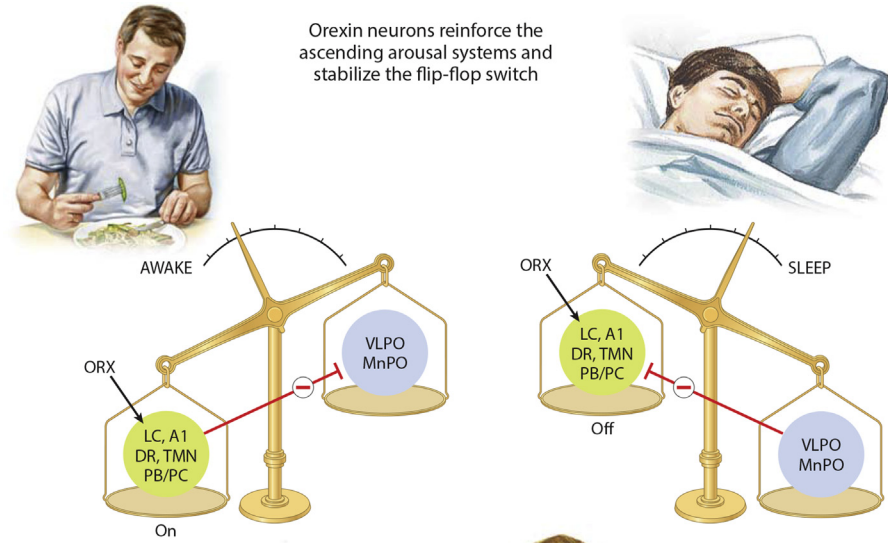
Narcolepsy symptoms include severe unremitting hypersomnolence with sleep attacks in 100% of patients, cataplexy (in 60%–70% of patients), sleep paralysis (in 25%–50%), hypnagogic hallucinations (in 20%–40%), disturbed night sleep (in 70%–80%), and automatic behavior (in 20%–40% of patients). Sleep attacks are defined as chronic and irresistible desire to fall asleep at inappropriate opportunities and in inappropriate places (eg, while driving, playing, eating), as illustrated in **Fig. 6**.<sup>64,65</sup> About a third of patients report 3 of the 4 major manifestations of the narcoleptic tetrad (sleep attacks, cataplexy, sleep paralysis, and hypnagogic hallucinations), and about 10% of patients describe all 4 major features occurring together.<sup>66,67</sup>

Cataplexy is pathognomonic for narcolepsy, and is defined as a sudden loss of skeletal muscle tone typically preceded by a prodromal powerful emotional stimulus, such as laughter, excitement, surprise, or anger, leading to a transient loss of skeletal muscle tone.<sup>64,65</sup> Episodes of cataplexy typically last from a few seconds to several minutes; may be partial or complete; and appear to an observer to consist of head nodding, sagging of the jaw, and buckling of the knees. However, consciousness is always preserved, and neurologic examination shows flaccidity of the muscles and markedly reduced or even absent skeletal muscle stretch reflexes. Cataplexy does not always present with the onset of hypersomnolence, but may manifest months to years after the initial onset of sleepiness.<sup>65</sup> Physiologically, during cataplexy, skeletal muscle weakness is generated by decreased excitation of noradrenergic neurons and increased inhibition of motor neurons by gamma-aminobutyric acid–releasing or glycinergic neurons.<sup>68</sup>

Sleep paralysis consists of paralysis of skeletal muscle tone, lasting from a few minutes to as long as 15 to 20 minutes, and occurs either during sleep onset or immediately on awakening. Patients describe frightening spells of complete paralysis, with inability to move or speak with preservation of consciousness. Hallucinations in narcolepsy occur during sleep onset (hypnagogic) or on awakening (hypnopompic) and are reported as vibrant and dramatic visual (and often fear-inducing) hallucinations but could also present as auditory, vestibular, or somesthetic.

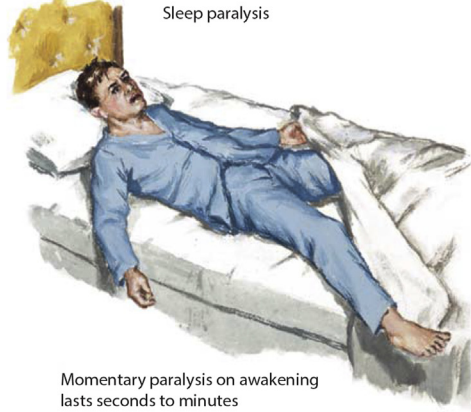
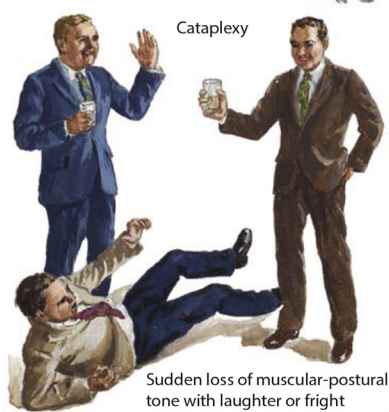
Narcolepsy is a manifestation of inability to maintain wakefulness during the day and, paradoxically, inability to maintain sleep during the night: although patients are pathologically sleepy during the day, as many as 70% to 80% report significant disruption of their ability to maintain sleep.<sup>65</sup> Automatic behavior in narcolepsy consists of repeated performance of a single monotonous, repetitive, routine task, such as writing, shopping, or driving, in a dull manner without conscious memory or awareness of the behavior.<sup>65</sup> Automatic behaviors in narcolepsy are thought to emerge from partial sleep episodes, frequent lapses, or microsleeps.

It has been established that HLA-DQB1\*0602 is a biomarker for narcolepsy across all ethnic groups. About 12% to 38% of the general population carries this HLA allele, whereas narcolepsy is present in only 0.02% to 0.18% of the population. Hypocretin



**Narcolepsy**

Excessive daytime sleepiness in narcolepsy or sleep apnea



**Fig. 6. Narcolepsy: A Hypothalamic Sleep Disorder.** Orexin/Hypocretin (ORX) ventrolateral preoptic nucleus (VLPO), Median preoptic nucleus (MnPO), tuberomammillary nucleus (TMN), the locus coeruleus (LC), parabrachial and precoeruleus (PB/PC) nuclei, Adenosine A1 Receptors (A1), dorsal raphe (DR).



levels are generally normal if the patient is HLA-DQB1\*0602 negative, unless the patient has a diencephalic lesion that explains the CNS hypersomnia-NT1 caused by a medical condition, as in the patient presented.<sup>63</sup>

The current underlying pathophysiology of narcolepsy-cataplexy syndrome is thought to manifest from an injury or degeneration, possibly through an autoimmune process, of the hypocretin neurons residing in the perifornical and lateral regions of the hypothalamus.<sup>69–71</sup> Narcolepsy-cataplexy syndrome (NT1) thus can be considered a hypocretin deficiency syndrome, which is how the condition is currently referred to in the updated version of the ICSD-III.<sup>63</sup>

The differential diagnosis of hypersomnia is extensive, but includes sleep deprivation and insufficient sleep syndrome (voluntary sleep curtailment); sleep disordered breathing (such as OSA); hypersomnias related to alcohol and medications; circadian rhythm sleep disorders (such as delayed sleep phase syndrome); and medical, neurologic, and psychiatric disorders causing hypersomnolence. Common neurologic diseases presenting with pathologic sleepiness include MS, myotonic dystrophy, and Parkinson disease.

OSA is the most common cause of hypersomnia in patients referred to a sleep laboratory for evaluation. Idiopathic hypersomnia (IH) overlaps with narcolepsy syndrome in that these patients are pathologically sleepy, but, in contrast with narcolepsy, the sleep episodes in IH are prolonged, and the sleep is not refreshing. Cataplexy should be differentiated from atonic seizures (as well as gelastic-atic seizures characterized by laughing followed by loss of muscle tone), drop attacks, basilar migraines, ver-tebrobasilar insufficiency, and syncope.

Management of narcolepsy consists of nonpharmacologic and pharmacologic treatment strategies.<sup>64</sup> Behavioral, or nonpharmacologic, treatments include scheduled short daytime power naps typically lasting between 15 and 20 minutes in the early to midafternoon; measures to enhance sleep hygiene, such as maintenance of a regular sleep schedule; and avoidance of sleep deprivation. Strategies to address excessive daytime sleepiness include the use of wake-promoting agents such as modafinil or armodafinil and stimulants such as methylphenidate, dextroamphetamine, or methamphetamine.<sup>64,72,73</sup> Treatment of cataplexy and other REM intrusion events of narcolepsy (such as sleep paralysis and hypnagogic hallucinations) depends on the frequency and severity of these episodes. For cataplexy, treatment with tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, or selective serotonin reuptake inhibitors (SSRIs) is helpful. However, sodium oxybate (gamma hydroxybutyric acid) is specifically indicated for the treatment of cataplexy as well as daytime sleepiness in the setting of NT1 and NT2.<sup>72,73</sup>

### **Summary of the Case Presentation**

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The patient presented with other manifestations of hypothalamic dysfunction, including inability to feed and regulate body temperature, and panhypopituitarism. He was witnessed to experience cataplexy later during the hospital course. The case is an example of symptomatic or secondary narcolepsy, terms used to describe narcolepsy associated with underlying structural, genetic, inflammatory, or vascular abnormality affecting the hypothalamus and leading to severe CNS hypersomnolence with or without cataplexy or abnormal CSF hypocretin levels. Depending on the presence of cataplexy or reduced CSF hypocretin levels, NT1 or NT2 may be diagnosed. As illustrated in **Fig. 5**, leading CNS causes of secondary narcolepsy include diencephalic and midbrain tumors, cerebrovascular disease, traumatic brain injury, MS, vascular malformations, encephalitis, cerebral trauma, and paraneoplastic syndrome with anti-Ma2.<sup>74–79</sup>

**CASE E: RESTLESS LEGS SYNDROME MANIFESTING WITH SLEEP-ONSET INSOMNIA, POOR QUALITY OF LIFE, AND EXCESSIVE SLEEPINESS**

Also known as Willis-Ekbom disease (WED), RLS is a sleep-related neurologic disorder that affects about 5% to 10% of the adult population. It has specific diagnostic clinical criteria and effective treatment strategies that make screening and management of this condition critical in sleep medicine practice.

**Case Presentation**

A 71-year-old man presents to the sleep disorders clinic with bothersome complaints of irresistible urge to constantly move his legs and significant sleep-onset insomnia occurring on a nightly basis. He is observed to engage in vigorous stretching and flexing of his legs, and to have difficulties remaining still during long drives and prolonged international flights to visit his daughter and her family, who live overseas. His wife describes that he constantly moves his legs back and forth in the evening and has bothersome and frequent leg jerks throughout the night. He is presenting to clinic because his symptoms are now intolerable. Activities that improve or alleviate the symptoms include stretching the legs, getting out of bed, walking, and massaging his legs. His wife says that the leg jerks also severely disrupt her sleep during the night.

**Clinical Questions**

1. What are the diagnostic criteria for RLS?
2. What is the most likely cause for the reported leg jerks?
3. What are the specific treatment strategies for RLS?
4. What are the key treatment-related side effects that must be reviewed with every patient with RLS?

**Discussion**

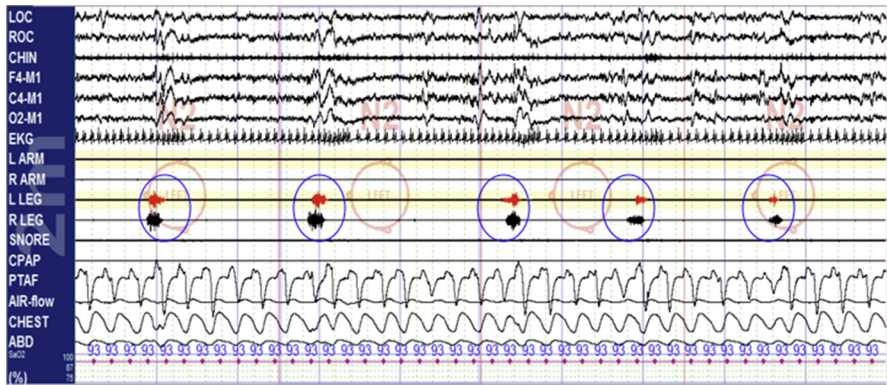
RLS is also known as WED, which credits the British physician Sir Thomas Willis (1621–1675), who first noted the disorder during his studies of the human nervous system, and the Swedish neurologist Dr Karl-Axel Ekbom (1907–1977), who originally named the condition RLS.<sup>80,81</sup>

Five essential diagnostic criteria used for diagnosing RLS/WED are (1) an urge or a compulsion to move the legs, (2) worsening of this discomfort in the evening, (3) temporary relief of the discomfort by movement, (4) worsening of symptoms during rest, and (5) symptoms that are not solely caused by another medical or behavioral condition.<sup>80,81</sup> The condition manifests as insomnia, and can significantly impair health-related QOL by worsening pain, vitality, and social functioning. The reduced QOL for individuals with RLS/WED is comparable with that of patients with serious chronic medical conditions, such as hypertension and diabetes.<sup>82,83</sup>

RLS is a prevalent sleep disorder, affecting about 10% of the general population<sup>84–86</sup> and often presents, as in the patient described earlier, with difficulties initiating sleep.<sup>87</sup> RLS is further classified into primary, if no identifiable cause can be established, or secondary, when a comorbid neurologic or medical condition is identified.<sup>88,89</sup> Patients with primary RLS/WED have greater than a 50% probability of having a first-degree relative with this condition.<sup>90–92</sup>

Up to 80% of patients with RLS/WED also experience undesirable nocturnal myoclonic movements known as periodic limb movements of sleep (PLMS), as shown in **Fig. 7**, consisting of rhythmic, stereotyped movements of the legs during sleep.<sup>93</sup> PLMS can be asymptomatic, or may induce sleep disruption, insomnia, and excessive daytime sleepiness. The combination of PLMS and symptoms of disrupted sleep is





**Fig. 7.** PLMS. A 2-minute sleep epoch from a diagnostic polysomnogram of a patient with PLMS associated with an irresistible urge to move her legs. Her husband reports that she has frequent nighttime kicking and jerking movements that disrupt his sleep. A succession of 5 periodic limb movements are shown (circled in purple), occurring in the right and left legs (anterior tibialis muscles). According to the American Academy of Sleep Medicine, periodic leg movements are diagnosed when more than 15 leg movements per hour of sleep are captured. Four or more consecutive movements are required and the interval between movements is typically 20 to 40 seconds. The movements should appear at sequence of 4 or more separated by an interval of more than 5 and less than 90 seconds and have an amplitude of greater than or equal to 25% of toe dorsiflexion during the calibration. Reference electrodes (F4, C4, O2) are referenced to mastoid electrode (M1) or average (AVG). ABD, abdominal respiratory effort; CHEST, chest respiratory effort; Chin, Chin electromyogram; EKG, electrocardiogram; L, left; LOC, left electro-oculogram; PTAF, nasal pressure; R, right; R LEG, right anterior tibialis surface electromyogram; ROC, right electro-oculogram; SNORE, snore sensor air flow, nasal and oral airflow; SpO<sub>2</sub>, pulse oximetry.

known as the syndrome of PLMDS. PLMDS represents a separate diagnosis from RLS, although the two frequently co-occur.

The pathophysiology of RLS/WED and PLMDS is based on studies of brain iron and dopamine metabolism, which suggest a CNS cause involving 3 major contributors to the disease: iron, dopamine (DA), and glutamate. However, recent data indicate that brain iron deficiency acting partially through hypoxic pathway activation, induces increased presynaptic and synaptic DA, which produces postsynaptic downregulation that overcorrects for the normal evening and nocturnal decrease in dopamine-promoting RLS/WED.<sup>94</sup>

The differential diagnosis of RLS/WED is critical to establish, because many other conditions, such as nocturnal leg cramps (NLC), positional discomfort, peripheral neuropathy, akathisia, and neurogenic and vascular claudication, can complicate the diagnosis by meeting 4 diagnostic criteria for RLS (1, 2, 3, and 4 mentioned earlier) and hence mimic RLS.<sup>95–97</sup> Definitive RLS/WED diagnosis now requires exclusion of these other conditions (criterion 5 listed earlier).<sup>95</sup> To further elucidate the differential diagnosis of RLS/WED, clinicians may ask patients about the circadian time predilection (which is often more specific to RLS), painful palpable muscle contraction or cramping (more unique to NLC), an inner body as opposed to peripheral restlessness in patients who are on neuroleptics drugs (more specific to akathisia), and amelioration with rest (symptomatic of vascular claudication).<sup>96,98,99</sup>

As mentioned earlier, the specific cause of the patient's leg jerks is most likely relate to PLMS, which are described as a series of stereotyped leg movements consisting of

dorsiflexion of the foot and extension of the big toe, occurring at a typical frequency of every 20 to 40 seconds throughout the night, but primarily during non-REM (NREM) sleep. Patients with PLMDS typically report disturbed sleep continuity, insomnia, reduced sleep quality, or hypersomnia secondary to nighttime arousals. Although PLMDS can be suspected based on a clinical history or reports by bed partners of disruptive limb movements, the condition requires formal polysomnographic diagnosis.

Management strategies for RLS/WED include both nonpharmacologic and specific pharmacologic intervention strategies.<sup>100,101</sup> Conservative, behavioral, nonpharmacologic approaches are appropriate first options and include the removal of medications or substances known to induce/worsen RLS/WED. Examples include discontinuation of substances such as tobacco, alcohol, and caffeine and removal of medications such as dopamine antagonists, antiemetics, lithium, and antidepressants (particularly SSRIs, tricyclic antidepressants).<sup>96,100–102</sup> Iron deficiency can exacerbate RLS symptoms and therefore iron should be supplemented if appropriate when serum ferritin levels decrease to less than 50 ng/mL (50 µg/L).<sup>96</sup> It is suggested that any patient with newly diagnosed RLS/WED or patients with RLS with a recent exacerbation of symptoms should have their serum ferritin levels measured and, when appropriate, supplemented with iron sulfate and, when clinically indicated, undergo an evaluation for iron deficiency.<sup>103</sup>

Specific drug therapy for patients with RLS/WED should be entertained for patients who described insomnia, daytime consequences, or poor sleep quality or duration. Prescribers should monitor for treatment-related side effects, and emergence of DA-specific side effects including augmentation, rebound, daytime somnolence, and impulse control behaviors (ICB). Management with DA and alpha-2-delta ligands are the most well studied and may represent the most appropriate first-line option for most patients who present with moderate to severe primary RLS/WED.<sup>100–102</sup> The FDA-approved dopamine agonists include ropinirole, pramipexole, and rotigotine, and the alpha-2-delta ligand gabapentin enacarbil.<sup>104,105</sup>

Specific drug class–associated side effects attributable to dopaminergic agents include nausea, hallucinations, hypotension, and ICB.<sup>106</sup> Augmentation refers to a geographic spread of sensory symptoms to previously unaffected body parts, as well as to onset of RLS/WED symptoms earlier in the day. The rates of these DA-specific side effects can be as high as 70% of patients treated with dopamine precursors (carbidopa, levodopa), especially in doses exceeding 200 mg.<sup>107</sup> Adverse effects of alpha-2-delta ligands generally include hypersomnolence, weight gain, and dizziness.<sup>105</sup> Alpha-2-delta ligands may be appropriate for patients with RLS/WED who have experienced significant comorbid insomnia and anxiety, and for those who have a history of, or report, DA-induced augmentation.

Benzodiazepines, particularly clonazepam, may be efficacious in RLS/WED and may also help patients with bothersome PLMDS, but are limited because of sedation and respiratory depression, which is particularly problematic for older adults.<sup>108</sup> Note that, as of February 2016, there are currently no FDA-approved treatments specifically to address PLMD.

### **Summary of the Case Presentation**

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Given that the patient reported frequent episodes of RLS/WED symptoms that affected his QOL, he was placed on a DA on a nightly basis, which completely resolved his symptoms and even reduced the leg jerks noted by his wife. However, a few weeks after initiating therapy, his wife, who was well informed about ICB, noted that he was

compulsively shopping online and spending hundreds of dollars each week on nonessential items. The patient was immediately switched to an alpha-2-delta ligand, which resolved his compulsive shopping and improved his nighttime and daytime symptoms arising from RLS/WED.

### **CASE F: RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER**

Patients who present with RBD are generally older men with potentially injurious nocturnal behaviors; these individuals have high rates of phenoconversion to a neurodegenerative disease.

#### ***Case Presentation***

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A happily married 65-year-old man presents with episodes of dream enactment since 2013 associated with flailing of the arms, kicking of the legs, thrashing, yelling, and screaming. One sleep episode resulted in kicking of his leg as if trying to kick a ball, leading to fracture of his right toe. Another spell involved punching of a thief in his dream, but resulted in punching of his wife, resulting in severe ecchymosis and zygomatic fracture. Since then, he has begun to sleep in a sleeping bag so as to protect himself from hurting himself and his wife. He was seen by his primary care physician who prescribed him clonazepam at night to help calm him down, at a dose of 0.25 mg, which contributed to 80% improvement within 2 weeks of therapy. He is on no other medications besides clonazepam and his general and neurologic examination are normal. His wife is apprehensive because she read on the Internet that people who fight during their dreams may develop Parkinson disease later in life.

#### ***Clinical Questions***

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1. What is RBD?
2. How is RBD diagnosed?
3. What are some specific treatment strategies for RBD?
4. What should your response be regarding the wife's concerns about RBD?

#### ***Discussion***

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Parasomnias are defined as abnormal and undesirable sensory, motor, or verbal phenomena that manifest during sleep or sleep-wake transition. Parasomnias are subdivided into episodes that occur during NREM sleep, also known as disorders of arousal, which include sleepwalking, sleep terrors, and confusional arousals.<sup>109,110</sup> REM sleep parasomnias consist of isolated sleep paralysis, nightmares, and RBD, for which memory is typically retained for the event on awakening, usually in the form of a dream.<sup>109-111</sup> REM sleep is accompanied by a loss of skeletal muscle tone throughout most of the body. However, in RBD, patients experience pathologic augmentation of skeletal muscle tone during REM sleep along with unusual, often complex, and sometimes vigorous, violent, and potentially injurious motor activity during the dream enactment sequence. The potential for patients to harm themselves and their bed partners, as in the patient described earlier, is high.<sup>112,113</sup>

The prevalence of RBD is about 0.5% of the population.<sup>114</sup> The disorder has a unique gender predilection, affecting male patients by a factor of 9, and is more likely to manifest in older patients, more than age 50 years. The reason for this gender predilection remains unclear.<sup>115-117</sup>

The diagnosis is suspected clinically, but must be confirmed by conducting a sleep study to show abnormal increase of chin or limb muscle tone during REM sleep with

synchronous complex motor activity associated with elaborate dream enactment that corresponds and synchronizes with the dream sequence (Fig. 8).<sup>112</sup> The spectrum of abnormal behaviors is wide, ranging from unpleasant hallucinatory behaviors to kicking, yelling, punching, and pugilistic or negative dream content often involving experiences of being confronted by an intruder requiring patients to defend or protect themselves.

#### REM SLEEP BEHAVIOR DISORDER

Patients who lose their ability to be paralyzed during REM sleep begin to act out their dreams and are usually unaware of these occurrences because the episodes occur during sleep. Often the first episodes are observed by the spouses of the patients.



**Fig. 8.** RBD. A patient with RBD presents with abnormal dream enactment behavior clinically, as manifested in this illustration of a man who is punching the wall, as in the case presented in the text, as if in a quasi-dream enactment flight/boxing match, with potential for injuries to self and bed partner.

However, many times it is the injury to the patient and the patient's bed partner that brings the patient to the attention of the clinician. When awoken from an episode, some patients have vivid recall and report dream mentation that correlates with the observed behavior. The frequency of RBD spells is variable from infrequent (ie, once a month) to as frequent as nightly. More frequent episodes lead to significant sleep disruption and are more likely to result in sleep fragmentation, hypersomnolence, and increased likelihood to translate to a referral to the specialist.<sup>118</sup> The potential for injury such as facial ecchymosis, skin lacerations, and skull fractures requires these patients to be evaluated and treated quickly. Safety concerns warrant immediate and effective pharmacologic interventions.<sup>118</sup>

RBD exists as 2 distinct phenotypes: an acute and a chronic form. The acute form of RBD is often encountered in younger patients (<50 years of age) and is likely related to antidepressant medication, substance abuse, CNS injury in the REM-generating neuronal network, and metabolic derangements. Common causes of drug-related and substance-related RBD include abrupt withdrawal of sedative-hypnotic agents, introduction of SSRIs, atypical antidepressants, tricyclic antidepressants, monoamine oxidase inhibitors, biperiden, and cholinergic medications.<sup>119–129</sup> Some case reports also link excessive caffeine consumption as a trigger.<sup>130,131</sup> Brainstem lesions caused by cerebrovascular accidents, MS, subarachnoid hemorrhage, and brainstem neoplasm have been all described as causes of the acute form of RBD.<sup>112,117,132–136</sup> The chronic form of RBD is typically seen in older patients (>50 years of age); most cases are idiopathic, and a minority are associated with neurodegenerative disorders.<sup>112</sup> A spectrum of dementias are implicated in RBD and include the alpha-synucleinopathies, including dementia with Lewy bodies with a characteristic alpha-synuclein inclusion in the nerve cell bodies.<sup>137</sup> The underlying mechanism of RBD is presumed to be related to abnormal brainstem control of medullary inhibitory regions.<sup>138</sup> Data from single-photon emission computed tomography neuroimaging reveal a potential mechanism relating to abnormalities in dopaminergic systems showing decreased striatal dopaminergic innervation as well as reduced striatal dopamine transporters.<sup>139–141</sup>

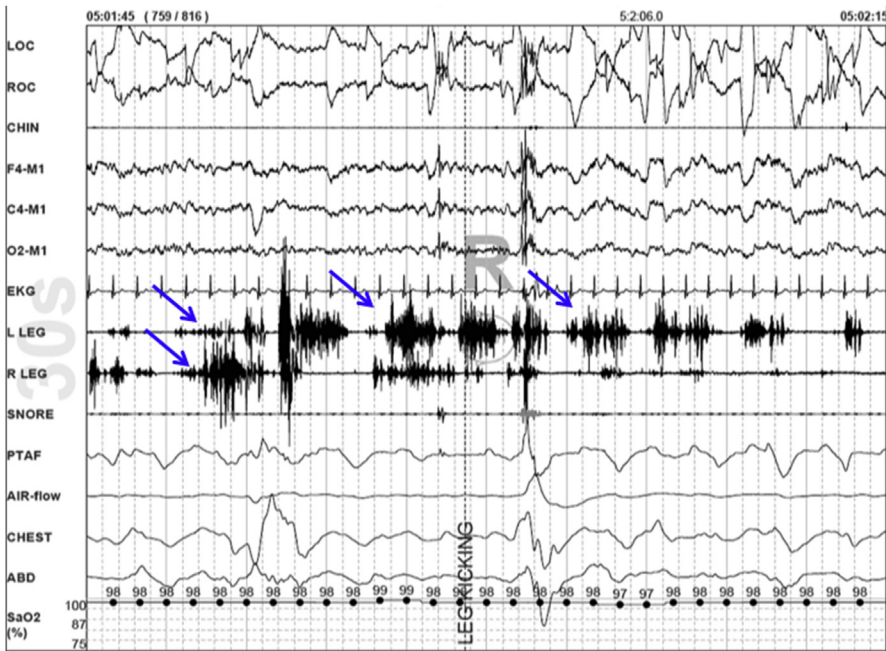
Polysomnographic data show increased and excessive muscle tone during REM sleep. According to the third edition of the ICSD-III, a diagnosis of RBD requires there to be repeated episodes of sleep-related dream enactment behaviors; these episodes can be documented by polysomnography to occur during REM sleep, or can be based on clinical history of dream enactment, which is presumed to occur during REM sleep.<sup>63</sup> Polysomnographic recording shows episodes of REM sleep without atonia, as shown in **Fig. 9**.<sup>142</sup> The last requirement indicates that the disturbance is not better explained by another medical, psychiatric, neurologic, or sleep disorder, or related to a medication or substance use.<sup>63,112</sup>

The differential diagnosis of RBD includes nocturnal frontal lobe seizures, confusional arousals, sleepwalking, sleep terrors, posttraumatic stress disorder, and nightmares.<sup>63,112,143</sup> Patient with RBD are often distinguished based on the complex nature of their episodes, timing later in the night when REM density is highest, and the characteristic patients who are older men.<sup>112</sup>

Patients with RBD should be assessed carefully with particular attention to risk for injury during the nocturnal episodes. The highest level of evidence for therapy calls for ensuring environmental safety (level A evidence), especially in patients (as in the case presentation) who experience injurious spells, displacement from bed, and aggressive behavior.<sup>144</sup>

Suggested level of therapy (level B evidence) lists 2 pharmacologic agents: clonazepam and melatonin.<sup>144</sup> The former is prescribed in typical dosages ranging from 0.25 mg to 1 mg by mouth at bedtime, achieving improvement in most (90%) patients





**Fig. 9.** Polysomnographic example of RBD. The specific abnormality in this 30-second epoch from a patient with RBD includes abnormally sustained muscle activity during REM sleep in which greater than 50% of the epoch reveals REM sleep without atonia, as indicated by the arrows pointing to the augmentation of electromyogram tone in the right and left legs (blue arrows). Reference electrodes (F4, C4, O2), referenced to M1 or AVG.

with little evidence of tolerance or abuse in this clinical context.<sup>145–148</sup> Treatment of RBD with melatonin 3 to 12 mg at bedtime is advantageous because it may restore REM sleep atonia and can be as effective as benzodiazepines.<sup>149–151</sup> Clinicians should be aware that melatonin is a dietary supplement, and is currently not approved by the FDA for any indications. Melatonin also has poor regulation in terms of pharmacologic preparation, and side effects have not been widely studied. Other drugs that may have some efficacy for RBD include imipramine (25 mg by mouth at bedtime), carbamazepine (100 mg by mouth 3 times daily) as well as pramipexole and carbidopa-levodopa.<sup>152–154</sup> Recent data from the Minnesota group suggest the use of an innovative alarm to reduce episodes of RBD in patients who may be refractory to traditional pharmacologic agents.<sup>155</sup>

An important prognostic observation is that RBD may precede the emergence of alpha-synucleinopathies by more than a decade.<sup>156–160</sup> Most patients with RBD eventually develop a neurodegenerative disorder from several months to decades after initial diagnosis in a dose-response pattern with a phenoconversion rate of approximately 50% every 10 years.<sup>137,142,161</sup> Given that RBD is an important biomarker of alpha-synucleinopathies, RBD represents a unique and powerful opportunity to screen patients and potentially treat those at risk with novel neuroprotective agents to help delay, if not reverse, the eventual evolution to dementia.<sup>162,163</sup>

### Summary of the Case Presentation

The patient was diagnosed with RBD based on the clinical features of his spells and polysomnography showing REM sleep without atonia. Although clonazepam was

prescribed in a serendipitous manner to treat aggression, it was the correct therapy. The issue of whether the condition could translate to a neurodegenerative condition later in life deserved closer observation. It is the authors' opinion, as those expressed in recent review of the ethical considerations in RBD, that the potential of risk-associated neurodegeneration should be disclosed and not hidden from patients and families.<sup>164</sup> In the spirit of transparency and disclosure of a diagnosis of RBD as well as disclosure of risk of the potential implications, given the risk, physicians should dedicate time to review the data and the possible emergence of future neurodegeneration, factor in the educational level of the patient and family, help to uncover potential fears, and clarify that the alpha-synucleinopathies are manageable conditions even if they do eventually manifest themselves.<sup>164</sup>

## SUMMARY

As shown by the patients discussed earlier, a variety of sleep disorders are highly prevalent among patients with neurologic diagnoses. Commonly associated conditions are comorbid OSA in the setting of epilepsy, insomnia in individuals with MS, advanced sleep phase circadian rhythm disorder in AD, NT1 in patients with hypothalamic injury, RLS in patients with peripheral neuropathy, and RBD in individuals with Parkinson disease. Often the neurologic condition contributes to the development of the sleep disorder, and if left untreated the sleep disorder may worsen the comorbid neurologic condition, showing a reciprocal relationship. It is therefore important for practitioners to maintain a high index of suspicion for sleep disorders in their patients with neurologic conditions.

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