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## NEUROLOGY BOARD REVIEW MANUAL

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## Sleep Medicine for the Neurologist

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# Sleep Medicine for the Neurologist

Rachel E. Salas, MD, and Charlene Edie Gamaldo, MD


## INTRODUCTION

Between 50 and 70 million Americans suffer from sleep disorders annually. These disorders account for an estimated \$16 billion in medical costs and over \$50 billion in indirect costs, including accidents, litigation, property destruction, hospitalization, and death.<sup>1-3</sup> Neurologists must have a good understanding of general sleep medicine since sleep disturbance and primary sleep disorders have been recognized as significant comorbid health concerns in stroke, epilepsy, neuromuscular disorders, movement disorders, neurodegenerative diseases, and headaches.<sup>4-12</sup> Patients who present with a sleep complaint can be divided into those with difficulty acquiring good quality sleep and those suffering from excessive daytime sleepiness (EDS). Common primary sleep disorders resulting in EDS include insufficient sleep, sleep-disordered breathing (SDB), circadian rhythm disturbance, narcolepsy, and idiopathic hypersomnolence. Common primary sleep disorders resulting in poor sleep quality include primary insomnia, restless legs syndrome (RLS), SDB, parasomnias, circadian rhythm disturbance, and periodic limb movement disorder (PLMD). Regardless of the sleep disorder, a thorough sleep history is pivotal to making the proper diagnosis and developing the most appropriate treatment plan for the individual (**Table 1**).

This manual reviews the diagnostic and therapeutic considerations surrounding sleep disorders in the context of 2 sleep disorder cases neurologists are likely to encounter in practice.

## CASE 1: A 53-YEAR-OLD WOMAN WITH DAYTIME SLEEPINESS

### INITIAL PRESENTATION AND EVALUATION

 A 53-year-old woman with a history of heavy snoring and EDS that has progressed over the last few years is referred by her primary care provider for a consultation with a general neurologist. She reports going to bed between 1 and 3 AM and is usually able

to fall asleep in less than 5 minutes. She reports 2 to 3 awakenings during the night for reasons that are unclear to her. She awakens at 6 AM with the use of an alarm clock. She reports obtaining 4 to 6 hours of sleep overall per night and always feels unrefreshed upon awakening. She takes scheduled naps throughout the day that are usually several minutes in length, after which she usually feels refreshed upon awakening. She has been snoring for at least 4 years per report from her significant other. Her score on the Epworth Sleepiness Scale is 21 out of a maximum of 24 (normal  $\leq 10$ ), which is suggestive of pathological sleepiness (**Table 2**).<sup>13</sup> She reports episodes of sleep paralysis that have increased in frequency over the last month. Moreover, she reports episodes of her tongue becoming weak and feeling as though she loses muscle tone when laughing. These events have been occurring since her early teens but have progressively worsened over time. However, these episodes are not associated with loss of consciousness, rhythmic movements, or bowel or bladder incontinence. On occasion, she sees “shadows” in her bedroom as she is falling asleep. Her past medical history is significant for depression only. She is postmenopausal. She denies any childhood sleep disorders. She currently works as a computer analyst 5 days a week (4 PM to 12 AM). She consumes at least 3 cups of caffeine-containing drinks throughout the day. She reports having a great deal of stress related to her work and home life. To help her relax at bedtime, she watches TV or works on the computer. She is a smoker and has 3 to 4 alcoholic drinks per month. Her family medical history is remarkable only for her father who snores.

On review of systems, the patient reports difficulty with irritability, memory, and concentration as well as chronic musculoskeletal pains. She reports a weight gain of approximately 10 lb over the past year (body mass index [BMI]  $> 25$  kg/m<sup>2</sup>). Her current medication list includes venlafaxine hydrochloride only. Her examination is remarkable for micrognathia and mild retrognathia. The oropharynx is crowded and shallow and her neck is short and thick. Examination of the extremities shows no signs of clubbing or cyanosis, although trace pitting edema bilaterally to the mid calves is noted.

- What are potential causes for this patient’s EDS?

**Table 1.** Approach to Taking a Sleep History

**When to take a sleep history**

- Not feeling rested upon waking from sleep
- Unable to initiate sleep at desired bedtime
- Unable to maintain sleep (ie, frequent awakenings)
- Experience excessive sleepiness during the day
- Snoring

**A general guideline for conducting a sleep history**

- How long has the sleep complaint been present?
- What is the bedtime routine?
- What are the evening medications?
- What is the average time to bed and amount of time to fall asleep?
- Are there any environmental (eg, snoring roommate) or physical factors (eg, pain, leg discomfort) that affect sleep initiation?
- How many awakenings occur during the sleep period?
- What are the identifiable triggers for the awakening (eg, nocturia, pain, snoring)?
- Are there reports of snoring, apnea, gasping for air, limb movements, or dream enactment?
- What is the average total sleep duration?
- Does the patient wake up with or without an alarm clock?
- How is daytime functioning (eg, recent accidents; job-related performance difficulties)?
- Does the patient take voluntary or involuntary naps; if so, how often?
- Does the patient tend to sleep-in on the weekends?
- What is the current medical and surgical history?
- What are the current medications; any recent changes?
- Any recent weight changes?
- If female, what is the menopausal status?

**DIFFERENTIAL DIAGNOSIS OF DAYTIME SLEEPINESS**

EDS is a common and nonspecific complaint that may result from a primary sleep disorder, the development or treatment of several medical and psychiatric conditions, or even from practicing poor behavioral sleep habits (Table 3).<sup>14</sup> Similar to most clinical cases of hypersomnia, several etiologies may explain this patient's symptoms either solely or in combination.

Chronic insufficient sleep remains the most common cause of sleepiness in the general population. This patient reports an average total sleep duration of 5 to 6.5 hours daily, far below the 7.5 to 8.5 hours of sleep currently recommended by the American Academy of Sleep Medicine (AASM).<sup>15</sup> Although, chronic insufficient sleep may not be the sole reason for her EDS, it certainly must be considered as a contributing factor.

Inadequate sleep hygiene is common and should be addressed in all patients with sleep complaints as a factor contributing to poor sleep quality that can result in EDS. This patient demonstrates several behaviors that are not conducive to sleep, including excessive caffeine intake

**Table 2.** Epworth Sleepiness Scale

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

- Would never doze = 0
- Slight chance of dozing = 1
- Moderate chance of dozing = 2
- High chance of dozing = 3

- Sitting and reading
- Watching TV
- Sitting inactive in a public place (eg, theater or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when the circumstances permit
- Sitting and talking to someone
- Sitting quietly after a lunch without alcohol
- In a car while stopped for a minute in traffic

NOTE: For each situation, probability of dozing is self-rated as none (0), slight (1), moderate (2), or high (3). A score of 8 is considered borderline and 10 or higher is abnormal.

Adapted with permission from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.

throughout the day, smoking, and watching TV and working on the computer close to bedtime.<sup>16</sup>

According to the International Classification of Sleep Disorders, 2nd edition (ICSD-2), the essential feature of circadian rhythm sleep disorders (CRSD) is a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.<sup>17</sup> This patient comfortably goes to sleep far beyond the typical adult bedtime of 10 to 11 PM and experiences extreme difficulty waking up. In other words, this patient's inherent "night owl" tendencies (go to sleep late and wake late) are in conflict with social and personal obligations that force her to wake earlier than her internal sleep-wake clock would prefer, which can eventually result in chronic sleep loss and functional impairment. Thus, CRSD must also be considered a potential etiology.<sup>18</sup> This type of CRSD is known as the delayed sleep phase type (DSPT). DSPT is more common in adolescents and young adults (7% prevalence) and occurs in only 0.7% of middle-aged adults.<sup>19,20</sup> The other common CRSD is the advanced sleep phase type (ASPT). In ASPT bedtimes are 3 or more hours earlier relative to desired or socially acceptable sleep and wake times. ASPT is reported less frequently than DSPT, with an estimated prevalence of 1% in middle-aged adults.<sup>19</sup>

Because depression commonly results in daytime fatigue and sleepiness, the patient's history of depression must be considered as a possible contributor to her

**Table 3.** Differential Diagnosis of Excessive Daytime Sleepiness

Sleep apnea	Drug dependence/abuse
Upper airway resistance syndrome	Medication side effects
Narcolepsy	Posttraumatic hypersomnia
Depression	Brain tumors
Periodic limb movements in sleep	Circadian rhythm disorders
Idiopathic hypersomnia	Endocrine disorders (eg, diabetes)
Withdrawal from stimulant	Anemia/iron deficiency
Insufficient sleep syndrome	

daytime somnolence. Moreover, insomnia is associated with depression and is considered an inclusive symptom in the diagnostic criteria.<sup>21</sup> In a recent study of patients with depression in full remission, sleep disturbance was an independent risk factor for depression recurrence.<sup>22</sup> A reciprocal relationship may exist whereby patients with insomnia have a higher risk of developing major comorbid depression, which underscores the importance of inquiring about mood stability in all patients presenting with hypersomnolence.<sup>18</sup>

SDB produces profound daytime sleepiness and is common, especially in men (prevalence 4%) and overweight individuals.<sup>18</sup> Because the prevalence of SDB in postmenopausal women is 3.9%,<sup>23,24</sup> menopausal status needs to be assessed during the evaluation. Patients should also be asked if they have respiratory symptoms at night, including snoring, choking, or gasping for air, and EDS. Additional risk factors for SDB aside from postmenopausal status demonstrated by this patient include a history of snoring, a BMI greater than 25, micrognathia, retrognathia, and having a crowded oropharynx.<sup>25,26</sup>

Narcolepsy should be considered in the differential diagnosis of patients with EDS. The history is key in identifying whether a patient exhibits symptoms suggestive of narcolepsy. In this case, the patient endorses all 4 of the classic clinical tetrad of narcolepsy symptoms: EDS, cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations. Cataplexy is believed to be the most specific symptom for narcolepsy (Table 4).

• **What diagnostic testing is recommended for this patient?**

The patient has all 4 symptoms of the narcolepsy tetrad as well as risk factors for SDB and should undergo PSG and a MSLT. The ordering of these tests is key since narcolepsy is a diagnosis of exclusion, and all other causes of pathological sleepiness must be first evaluated and considered as potential contributing causes (sleep apnea, CRSD, and chronic sleep loss)


**Table 4.** Narcolepsy Tetrad

Narcolepsy Symptoms	Sensitivity	Specificity
Excessive daytime sleepiness	100%	Low
Cataplexy	60%–70%	Virtually 100%
Hallucinations		
Hypnopompic	30%–60%	Very common with sleep loss
Hypnagogic	30%–60%	Not specific
Sleep paralysis	25%–50%	Not specific (can be seen in other sleep disorders)

before the diagnosis is made.<sup>14,17</sup> To assess for CRSD, phase delay type, the patient should complete daily sleep logs over the course of 1 month. Although not required to make the CRSD diagnosis, sleep logs and tools such as actigraphy can provide supportive evidence for the diagnosis.<sup>27</sup> To objectively assess daytime somnolence, a PSG should be performed on the night immediately prior to a MSLT. In order to pursue a MSLT, the PSG should not reveal any obvious cause of EDS such as SDB that would explain a patient's clinical complaints.<sup>28</sup> To ensure that the patient is not chronically sleep deprived prior to performing the MSLT, sleep logs demonstrating at least 7.5 to 8.5 hours of sleep daily should be recorded for a minimum of 1 week prior to the laboratory assessment.

The MSLT is a well-validated and extensively published objective measure of the tendency of a subject to fall asleep under standardized laboratory conditions. The MSLT involves 4 or 5 nap periods, each 2 hours apart, with sleep-study monitoring to objectively assess the degree of sleepiness and evidence of decreased REM latency during daytime naps. It is conducted using a standardized protocol (Table 5 and Table 6) in which the patient is given a set of directions before undergoing each nap trial in order to maintain reliability and optimize interpretability of the results.<sup>29</sup> Prior to performing the MSLT, patients should be weaned from all medications that may affect sleep architecture (venlafaxine in this case) for at least 2 weeks (Table 7).

**FURTHER EVALUATION AND DIAGNOSIS**

 The potential etiologies considered in the differential are discussed with the patient. Upon further questioning, she feels that her depression is well controlled with venlafaxine hydrochloride and may not be a major factor in her EDS. Sleep hygiene tips as well as the importance of obtaining a minimum of 7.5 to 8.5 hours of sleep are emphasized, and the patient agrees to begin implementing these practices immediately. For

**Table 5.** Testing Conditions for the Multiple Sleep Latency Test (MSLT)

5 nap opportunities at 2-hr intervals; if 2 REM-onset naps or no REM onset naps occur in the first 4 nap sessions, then the MSLT can be stopped after 4 naps

The first nap should be 1.5 to 2 hr after the patient awakens from the nocturnal polysomnography test

Sleep logs should be obtained at least 1 wk prior to MSLT

Stimulants and REM-suppressing medications should be stopped 2 wk before MSLT

Drug screening should be done on the morning of the MSLT

Patient should not smoke or engage in vigorous physical activity 30 min prior to MSLT; caffeine and bright light exposure should also be avoided

Patient should be instructed to lie quietly, assume a comfortable position, close eyes, and try to fall asleep during each nap

REM = rapid eye movement.

Adapted with permission from Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113–21.

2 weeks before her sleep studies, the patient maintains a sleep log, which demonstrates at least 8 hours of sleep nightly with a consistent sleep/wake schedule (she is no longer working her late evening shift). The sleep architecture on the extended PSG demonstrates delayed sleep initiation with normal sleep efficiency ( $[\text{Total sleep time}/\text{Time in bed}] \times 100$ ) and normal REM latency (as defined by time to enter REM after falling asleep, normal = 45–120 min). Percentage of total sleep time spent in stage 1 and stage 2 of sleep is normal; however, she spends an increased amount of time in REM sleep and a decreased amount of time in slow-wave sleep relative to adult norms. She has 127 periodic leg movements during non-REM sleep with an index of 13.3 (events/hr). There is no evidence of SDB. Because her PSG does not demonstrate significant SDB or any other explanation for her degree of sleepiness, an MSLT is pursued the next morning. The results of the MSLT reveal a mean sleep latency of 1.3 minutes across the 5 naps. She has 2 REM-onset naps (REM entered within 15 min of sleep onset), occurring 0.5 minutes after sleep onset on one nap and after 1 minute of sleep onset on the third nap trial. Thus, due to the significantly reduced mean sleep latency and presence of early-onset REM sleep on 2 naps, the MSLT report is interpreted as severe reduction in daytime alertness. The final diagnosis is narcolepsy with cataplexy and periodic limb movements during sleep (PLMS).

### **NARCOLEPSY**

Narcolepsy affects between 0.03% and 0.1% of the general population. In most cases, the syndrome is

**Table 6.** Key Elements of Multiple Sleep Latency Test (MSLT) Interpretation

Sleep onset for clinical MSLT is determined by the time from lights out to the first epoch of any sleep stage

Absence of sleep during a nap opportunity is recorded as sleep latency of 20 min (this latency is included in the calculation of mean sleep latency)

To assess for the occurrence of REM sleep, MSLT should continue for 15 min from the first epoch of sleep

The duration of 15 min is by “clock time” (not by sleep time)

REM latency is taken as the time of the first epoch of REM sleep

A mean sleep latency of < 5 min is consistent with narcolepsy

16% of normal individuals have a mean sleep latency < 5 min

16% of patients with narcolepsy have a mean sleep latency > 5 min

REM = rapid eye movement.

presumed to develop sporadically, but there is a 1% to 2% chance that a patient with narcolepsy will have an affected child.<sup>30,31</sup> The prevalence of narcolepsy with cataplexy in Western European countries and North America approaches 0.05% (1 case per 2000 persons).<sup>31</sup> Narcolepsy commonly begins near adolescence, suggesting a precipitating role for the hormonal changes surrounding puberty. Interestingly, aging can affect symptom severity, as many patients with narcolepsy experience improvement in cataplexy with advancing age. The peak incidence of narcolepsy is seen in patients aged 15 to 30 years. Narcolepsy manifests before age 25 years in 70% to 80% of patients.<sup>32</sup> Interestingly, approximately 5% of cases have an onset after age 50 years.

The ICSD-2 defines narcolepsy as a disorder characterized by EDS.<sup>17</sup> The complaint of EDS occurring almost daily for at least 3 months is the essential feature for the diagnosis of narcolepsy. Two narcolepsy variants recognized are narcolepsy with cataplexy and narcolepsy without cataplexy. A third diagnosis, narcolepsy due to a medical condition, is used when the criteria for narcolepsy are met and the onset of the disorder appears to be the consequence of a medical condition, such as multiple sclerosis, amyotrophic lateral sclerosis, or stroke. Narcolepsy due to a medical condition may occur with or without cataplexy.

- **How is the diagnosis of narcolepsy made?**

### **Diagnosis**

When an individual presents with symptoms suspicious for narcolepsy, the clinician must obtain a careful history that should include a subjective assessment of the degree of EDS (Epworth Sleepiness Scale), a determination of the presence of cataplexy, and documentation of other elements of the narcolepsy tetrad.

**Table 7.** Rapid Eye Movement (REM) Sleep Suppressants

Tricyclic antidepressants (all but clomipramine)	REM sleep suppression
Mirtazapine	REM sleep suppression
Chloral hydrate	REM sleep suppression
Duloxetine	Increases slow wave sleep and REM sleep suppression
Venlafaxine and reboxetine	REM sleep suppression
Alcohol	Reduced REM density in the beginning of the night
Paroxetine	REM sleep suppression and increased REM latency
Thienobenzodiazepine-olanzapine	REM sleep suppression and increased REM latency
Monoamine oxidase inhibitors	REM sleep suppression
Lithium carbonate	Increases slow wave sleep and REM sleep suppression

Adapted with permission from Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. *Hum Psychopharmacol* 2005;20:533–9.

A detailed history documenting the pattern of EDS is essential (eg, frequency, onset, associated conditions that trigger symptoms). Fragmented sleep is also commonly reported in narcolepsy, resulting in the clinical “pentad” that combines this subjective complaint and PSG finding with the 4 classic narcolepsy symptoms. Automatic behaviors, depression, headaches, and frequent psychosocial problems are other less common features associated with narcolepsy. The symptoms in the tetrad represent normal physiologic features of REM sleep that abnormally intrude upon the wake state in patients with narcolepsy. Of note, not all these symptoms are present in every patient diagnosed with narcolepsy.

Other diagnostic possibilities that can cause EDS should be considered when evaluating patients with possible narcolepsy (Table 3). The most common are sleep-related breathing disorders and behaviorally induced insufficient sleep syndrome. Idiopathic hypersomnia is a disorder of unknown etiology that manifests as EDS but has none of the features of disassociated REM sleep seen in narcolepsy. Patients with this disorder often exhibit pathologic sleepiness on the MSLT, but usually no more than 1 REM-onset nap. Furthermore, they may respond to stimulants in a manner similar to patients with narcolepsy. It is also important to remember that fatigue associated with depression and other affective disorders may be mistaken for narcolepsy. Inquiry about use of drugs that can cause drowsiness is essential.

After considering and evaluating for other potential contributing etiologies for EDS, the diagnosis of narcolepsy is made based on clinical features and supportive objective evidence from the MSLT and PSG (Table 8). A mean sleep latency of 8.5 minutes or less across the 4 or 5 naps and the presence of 2 REM-onset naps on the

**Table 8.** Sensitivity and Specificity of Findings for the Diagnosis of Narcolepsy

	Sensitivity (%)	Specificity (%)
Multiple sleep latency test with:		
2 or more SOREMPs	80	93
2 or more SOREMPs and MSL < 5 min	70	97
3 or more SOREMPs	48	98.4
3 or more SOREMPs and MSL < 5 min	46	99.2
2 or more SOREMPs and MSL < 8 min	78	95
3 or more SOREMPs and MSL < 8 min	48	98.7
PSG with:		
SOREMP	29	98.5
SOREMPs and sleep latency (on PSG) < 10 min	27	98.9

Adapted with permission from Aldrich MS, Chervin RD, Malow BA. Value of the multiple sleep latency test (MSLT) for the diagnosis of narcolepsy. *Sleep* 1997;20:620–9.

MSL = mean sleep latency; PSG = polysomnography; SOREMPs = sleep onset rapid eye movement periods.

MSLT along with the appropriate clinical presentation are highly suggestive of narcolepsy. Key PSG features typical of patients with narcolepsy include short sleep latency (< 5 min), reduced REM latency (< 20 min), and sleep fragmentation. The disruption of sleep is characterized by numerous arousals for no apparent reason, increased stage 1 sleep, and reduced sleep efficiency. If PSG and MSLT cannot be obtained or would be invalid because of medications or other circumstances (Table 5 and Table 6), assessment of hypocretin levels in the cerebrospinal fluid (CSF) during the day should be considered. However, measurement of CSF hypocretin is not routinely done or needed to make the diagnosis.<sup>33</sup> Findings in narcolepsy without cataplexy have not been consistent. Because blood levels do not correlate with the CSF levels, serum tests for hypocretin are not useful.<sup>14</sup>

### Tetrad of Narcolepsy Symptoms

Because narcolepsy is a clinical diagnosis of exclusion, it is essential for physicians to feel comfortable recognizing the specific nuances of each of the tetrad symptoms. This section discusses each symptom separately.

**Excessive daytime sleepiness.** Patients with sleepiness due to narcolepsy typically report an onset in their teens or early 20s. A report of true EDS is noted that is consistent with falling asleep in inappropriate settings or the inability to stay awake. The sleepiness is similar to that experienced after extended sleep deprivation, as opposed to the fatigue one might report with chronic fatigue syndrome, depression, or chronic disease. The

sleepiness is usually improved by napping and typically has an adverse effect on all aspects of life (school, work, personal relationships). It is important to ask the patient and family members for specific examples of inappropriate sleep, such as at work, during social occasions, or while driving since patients often underreport or do not fully recognize the impact of sleepiness on their daytime function.

**Cataplexy.** Cataplexy is defined as a sudden loss of muscle tone provoked by strong emotion. Both REM sleep and cataplexy are characterized by atonia. Firing of the motor neuron causes muscle contraction, and muscle tone is maintained by asynchronous sustained firing of motor neurons. The atonia that occurs during REM sleep results from the postsynaptic inhibitory action of glycine on spinal cord interneurons, which leads to hyperpolarization of the motor neurons and loss of muscle tone and monosynaptic reflexes, such as the H-reflex, during REM sleep.<sup>33</sup> In narcolepsy, this normal physiologic process of muscle atonia in REM sleep (that prevents dream enactment and subsequent injury) is not limited to REM sleep but can inappropriately occur during wakefulness and result in sleep paralysis or cataplexy.

Although cataplexy is considered the most specific narcolepsy symptom,<sup>34</sup> it alone is not sufficient to diagnose narcolepsy. As much as 25% of the general population reports occasional episodes of muscle weakness triggered by emotions. Key factors in differentiating cataplexy from other nonspecific episodes of emotion-related muscle weakness are the triggers. Patients with narcolepsy typically have cataplexy triggered by a sudden emotional response to situations that elicit surprise, laughter (eg, when hearing a joke or being tickled), excitement, or anger.<sup>35</sup> Stress, fear, or emotions associated with physical activity such as running, sports, or sex are not specific triggers for narcolepsy. Moreover, episodes of cataplexy are usually brief, lasting seconds to a few minutes. They are generally bilateral and may affect any voluntary muscle, but the diaphragm is usually spared.<sup>18</sup> Knee buckling or leg weakness is most frequently reported.<sup>35</sup> Nevertheless, the site most specific for cataplexy is the face and head, where cataplexy may manifest as jaw sagging, facial flickering (involuntary trembling of facial muscles), or head drooping. Interestingly, patients with cataplexy only occasionally collapse to the ground and rarely sustain an injury, mainly because they can sense when the event is about to develop, giving them ample time to find a safe place to sit or rest through the event. Consciousness is typically maintained at the start of the episode, but an episode of sleep may follow cataplexy. Because these sleep episodes may be difficult to distinguish from the postictal confusion and fatigue that follow some seizures,

it is always important to solicit for any history suggestive of epilepsy. With seizures, amnesia for the events, rhythmic and/or dystonic movements, tongue lacerations, and/or bowel or bladder incontinence may occur. Seizures are not usually emotionally triggered, which can help serve as a differentiating clue. Cataplexy usually presents 3 to 5 years after onset of pathological sleepiness.

**Hypnagogic and hypnopompic hallucinations.** Hallucinations occurring at sleep onset (either at night or during daytime naps) are referred to as hypnagogic hallucinations. Hallucinations occurring during awakening from sleep are referred to as hypnopompic hallucinations. Hypnopompic hallucinations are thought to be more characteristic of narcolepsy; however, both types may be observed.<sup>18</sup> Visual hallucinations usually consist of simple forms.<sup>18,36</sup> However, hallucinations can be vividly realistic such that the patient acts on them upon awakening. Auditory hallucinations can also occur and range from elaborate melodies to someone talking.<sup>18</sup>

**Sleep paralysis.** Occurring in approximately 50% to 60% of narcolepsy patients, sleep paralysis is a potentially terrifying experience in which an individual is unable to move limbs, speak, or breathe deeply while remaining fully aware of the episode. It occurs upon falling asleep or upon awakening, and patients are able to recall the episode later, differentiating it from seizure-type activity. Anxiety may provoke these episodes initially, but with time most patients learn that the episodes are benign, usually lasting less than a few minutes with spontaneous resolution. Sleep paralysis may also occur as an independent and isolated phenomenon in 3% to 5% of the normal population, in whom it is usually triggered by sleep deprivation.<sup>18</sup> Recurrent isolated sleep paralysis is less common and is listed as a parasomnia associated with REM sleep in the ICSD-2 in which recurrent episodes of sleep paralysis occur without the other features or symptoms typically seen in patients with narcolepsy.<sup>17</sup>

- **What comorbid conditions are commonly found in patients with narcolepsy and other primary sleep disorders?**

#### **Comorbid Conditions**

PLMS are defined as rhythmic movements of the limbs occurring every 4 to 90 seconds with a duration of 0.5 to 10 seconds in length. PLMS are a common and nonspecific PSG finding seen as a normal variant of aging, in narcolepsy patients, and in a number of other medical, neurologic, and sleep conditions (**Table 9**). When present, PLMS should be noted since they can reflect a greater degree of disrupted sleep at night, which can impact daytime functioning.<sup>37</sup> These limb movements

**Table 9.** Conditions Associated with Periodic Limb Movements of Sleep

Aging*	Parkinson's disease
Narcolepsy	Spinal cord lesion
Restless legs syndrome	Rheumatic diseases
Sleep apnea	Posttraumatic stress disorder and attention deficit hyperactivity disorder
Iron deficiency anemia	
Pregnancy	Chronic obstructive pulmonary disease
Neuropathy	
Chronic renal failure	
Drugs (ie, neuroleptics and antidepressants)	

\*Present in 30% of individuals > age 50 yr.

may be treated with medications such as dopaminergic agents, but treatment will not improve the other symptoms of narcolepsy and may even exacerbate sleepiness.<sup>38</sup> When the PLMS appears to be associated with sleep disruption and negative daytime symptoms (not otherwise explained by another sleep condition), the diagnosis of PLMD can be made and treated accordingly. Commonly prescribed medications for PLMS/PLMD include dopaminergic agents (levodopa, ropinirole, pramipexole, carbidopa/levodopa) and  $\gamma$ -aminobutyric acid agonists (benzodiazepines such as clonazepam and temazepam and most sedative hypnotics). The presence of cataplexy and REM-onset naps on the MSLT distinguish patients with narcolepsy from those with PLMD.

Recent findings suggest that individuals with primary sleep disorders report a higher prevalence of mood disorders. For example, patients with sleep apnea or narcolepsy appear to have elevated levels of anxiety, depression, and substance abuse.<sup>39</sup> Patients with mood disorders should be screened for primary sleep disorders, and conversely all patients with sleep complaints should be screened for mood disorders.<sup>18</sup> These patients may also be at higher risk for other sleep disorders such as REM behavioral sleep disorder and sleep apnea.

### Pathophysiology

In recent years, most of the landmark findings uncovering the pathophysiology of narcolepsy have come from studies of canine narcolepsy cases. Canine narcoleptics exhibit cataplexy (triggered by emotional reaction to food or play), sleep-onset REM periods, and short sleep latency during a procedure equivalent to MSLT trials, and subsequently demonstrate symptom improvement with drugs used to treat narcolepsy in humans. The genetic defects responsible for canine and mouse narcolepsy have been identified. The gene for canine narcolepsy was identified by position cloning as the hypocretin receptor 2 gene (Hcrtr2) on dog chromosome 12.<sup>40</sup> Furthermore, mouse

narcolepsy is associated with deletion of the hypocretin peptide genes.<sup>41</sup> Hypocretin (also known as orexin) neurons are found in the hypothalamus and project to many different parts of the brain, including areas that regulate wakefulness. Activation of hypocretin/orexin neurons increases dopamine and norepinephrine in these areas and release of histamine from the tuberomammillary neurons. Animal studies have shown that animals with defective hypocretin/orexin systems show signs and symptoms similar to narcolepsy. These 2 findings implicate the hypocretin/orexin system in the pathophysiology of narcolepsy and the regulation of REM sleep (Table 10). On the other hand, most human narcolepsy cases presumably result from a loss of hypocretin/orexin production, as studies have shown significantly reduced numbers of hypocretin/orexin-producing cells in hypothalamus biopsy samples postmortem.<sup>42,43</sup>

The association between human leukocyte antigens (HLA) and narcolepsy was described in 1983.<sup>44,45</sup> The first marker identified, HLA-DR2, occurs in 85% to 98% of all white patients with narcolepsy-cataplexy; however, the association is weaker in the black population. Across all ethnic groups, HLA DQB1\*0602 has the strongest association with the development of narcolepsy, occurring in 85% to 100% of individuals with typical cataplexy.<sup>31,46</sup> However, it is currently believed that the presence of HLA-DR2 or DQB1\*0602 alone is not sufficient to cause narcolepsy, and additional factors likely play a role. Several environmental factors have been postulated. For example, an unknown antigen such as a virus could bind with the HLA molecule and presumably trigger a subsequent autoimmune response against the hypocretin/orexin cells, which are known to be destroyed in the development of narcolepsy. Although most other HLA-associated disorders are autoimmune in nature, there is no other definitive evidence demonstrating that narcolepsy has an autoimmune etiology. Furthermore, IgG oligoclonal bands are not present in narcolepsy patients, nor is there evidence of cellular autoimmunity.<sup>47</sup>

Other possible factors involved in the development of narcolepsy include changes in the neuroanatomical or neurochemical pathways associated with narcolepsy due to head trauma or toxin exposure. Disturbed sleep and profound psychological stress have also been reported to precipitate narcolepsy.<sup>48</sup> Studies of the role of heritability have found that familial clustering occurs in approximately 10% of narcolepsy cases. However, the specific cause of narcolepsy remains speculative.

### Treatment

Therapy is aimed at adequate control of the symptoms of narcolepsy with the goal of improving daytime

**Table 10.** Neurotransmitters of Sleep

Neurotransmitter	Wake/REM	Non-REM	Origin	Projections
GABA	(↓↓↓)/↑	↑↑↑	Brain stem ARAS, thalamus, hypothalamus, basal forebrain, cortex	Posterior hypothalamus, ARAS, thalamus
Adenosine	Increase with wakefulness/↑↑	↑↑↑↑	Diffuse cortical by-product of wake state	Brain stem and basal forebrain cholinergic cells
Histamine	↑↑↑↑/↑	↑↑	Tubero-infundibular (posterior hypothalamus)	Thalamus, brain stem
Acetylcholine	↑↑↑↑/↑↑	↑	Basal forebrain, LDT, PPT	Thalamus, posterior hypothalamus, basal forebrain
Norepinephrine	↑↑↑/(↓)	↑↑	Locus coeruleus	Cortex, hippocampus, thalamus, hypothalamus
Serotonin	↑↑↑/(↓)	↑	DRN	Same as norepinephrine
Hypocretin/orexin	↑↑↑↑/?	↑	Lateral and posterior hypothalamus	Locus coeruleus, DRN, LDT, PPT

NOTE: ↑↓ The direction of the arrow signifies the neurotransmitter's relative degree of activity/presence during the respective sleep stages. ARAS = ascending reticular activating system; DRN = dorsal raphe nucleus; GABA =  $\gamma$ -aminobutyric acid; LDT = laterodorsal tegmental nuclei; PPT = pedunculopontine tegmental nuclei.

functioning and optimizing quality of life. Effective therapy for narcolepsy is usually multifaceted, involving pharmacologic therapy, behavioral interventions (eg, maintenance of good sleep hygiene), and psychosocial and educational support. The US Food and Drug Administration (FDA) has approved 3 drugs for treatment of narcolepsy: modafinil and armodafinil for EDS and sodium oxybate for cataplexy and EDS (Table 11).

Stimulants are the only medications shown to be effective for treating the EDS associated with narcolepsy (with the exception of sodium oxybate).<sup>49</sup> Medications currently recommended as effective stimulants in the treatment of narcolepsy include modafinil, armodafinil, methylphenidate, methamphetamine, and dextroamphetamine. Amphetamines and amphetamine derivatives promote wakefulness by inhibiting the vesicular monoamine transporter, thereby increasing dopamine release and reducing presynaptic dopamine stores.<sup>50</sup> Mazindol also induces wakefulness by inhibiting dopamine reuptake at the synaptic cleft. Armodafinil is a longer-acting isomer of modafinil that was approved in 2007 for treating EDS. Although modafinil and armodafinil have wake-promoting effects similar to the amphetamine derivatives, their mechanism of action is debated. Recent evidence suggests that modafinil may activate hypocretin/orexin neurons, thus promoting wakefulness.<sup>51</sup> Modafinil also promotes wakefulness in animals who lack hypocretin/orexin receptors, suggesting that hypocretin/orexin activation is not absolutely required for the effects of modafinil.<sup>51,52</sup> Modafinil also appears to increase histamine release in the anterior hypothalamus of rats, suggesting that multiple mechanisms may be responsible for its promotion of wakefulness.<sup>51</sup>

Sodium oxybate can also be used to reduce EDS.<sup>43</sup> However, one must be aware of this medication's black

**Table 11.** Treatment of Narcolepsy

Behavioral	Pharmacologic (continued)
Schedule naps	Cataplexy
Avoid sedentary activities	Imipramine, clomipramine
<b>Pharmacologic</b>	Selective serotonin reuptake inhibitors
Sleep attacks (excessive daytime sleepiness)	Sodium oxybate*
Methylphenidate*	Disturbed/fragmented sleep
Dexamphetamine*	Benzodiazepines
Modafinil*	Benzodiazepine receptor agonists
Armodafinil	
Sodium oxybate	Sodium oxybate*

\*Approved by the US Food and Drug Administration.

box warning regarding its abuse potential and the need to avoid alcohol and other CNS depressants while taking sodium oxybate. Abuse has been associated with some important CNS adverse events, including death, confusion, depression, respiratory depression, and other neuropsychiatric events. The precise mechanism by which sodium oxybate produces its effects is unclear. One component of its activity may be to improve the restorative nature of nocturnal sleep and thereby reduce symptom severity.

Because of the intermittent nature of cataplexy and the variability in severity, not all patients require therapy for this symptom. The decision to treat is based on severity, frequency, impact on the patient's perception of functioning, medication tolerance, and consideration of possible side effects complications. Drugs that suppress REM sleep, most often non-sedating antidepressants, have been used historically to treat cataplexy. Sodium oxybate, the only FDA-approved medication for cataplexy, can also be considered. Sedatives may be used to treat fragmented sleep.

**Table 12.** Common Daytime Deficits Associated with Insomnia

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Fatigue, sluggishness, malaise
Attention, concentration, or memory impairment
Social or vocational dysfunction or poor school performance
Mood disturbance or irritability
Daytime sleepiness
Motivation, energy, or initiative reduction
Proneness for errors or accident at work or while driving
Tension headaches or gastrointestinal symptoms in response to sleep loss
Concerns or worries about sleep

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### Impact of Long-Term Therapy

Pharmacologic therapy to treat narcolepsy symptoms is often life-long, which raises multiple issues for the long-term management of these patients. As with any chronic medication, there are high rates of nonadherence, especially in adolescent patients.<sup>53</sup> Tolerance to the alerting effects of stimulants appears to occur with variable frequency, with reported rates from 0% to 40%.<sup>54</sup> Tolerance can lead to underdosing of stimulant medication, as can clinician hesitancy to use higher doses. Several studies have shown, however, that the abuse rate of stimulants among patients with narcolepsy is low.<sup>55</sup> The presence of other medical, psychiatric, or sleep disorders that lead to disruption of sleep or sleep deprivation can also negate the effects of stimulants.


All of the medications used to treat narcolepsy are metabolized by the liver, which can influence the pharmacokinetics of other hepatically metabolized medications, such as anesthetics and pressor agents. Patients with narcolepsy may be at higher risk of having apneic episodes, cataplexy, and sleep paralysis when recovering from inhalation anesthesia. Recreational drugs can similarly interfere with the efficacy of narcolepsy medications. Pharmacokinetic issues associated with narcolepsy treatment are particularly important when treating female patients of child-bearing age, as oral contraceptives may be less effective during treatment. These patients therefore require counseling and possibly additional contraceptive barriers.<sup>56</sup> It is also important to counsel narcoleptics regarding certain drugs that may aggravate cataplexy such as prazosin, trazodone, and nomifensine.

### Prognosis

Sleepiness is often a lifelong problem, although symptoms may fluctuate and improve with age in one third of patients. Narcolepsy patients have a normal lifespan but are more prone to accidents due to EDS and/or cataplexy, which can be fatal.<sup>14</sup> These patients

may also be at higher risk for other sleep disorders such as REM behavioral sleep disorder and sleep apnea.

### PATIENT FOLLOW-UP


 After initiation of modafinil along with implementation of better sleep hygiene rituals, the patient now obtains 8 hours of sleep on a consistent sleep/wake cycle. She is counseled regarding potential comorbid sleep disorders that may be encountered in the future as well as symptoms that are often associated with them so they can be identified and appropriately treated should they arise.

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## CASE 2: TOO LITTLE SLEEPING AND TOO MUCH EATING

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### INITIAL PRESENTATION AND HISTORY

 A 66-year-old woman presents to a sleep center with a 14-year history of insomnia due to “creepy crawly things in her legs associated with the urge to just keep moving.” These sensations regularly begin between 8 and 9 PM. While the patient is in bed, the sensations are often so intense that she is forced to get up and walk as the sole means of relief. Her bed partner describes her as an “active sleeper,” with reports of kicking, thrashing, gasping, and snoring throughout the night. In the morning, she wakes feeling unrefreshed and has difficulty functioning during the day (memory, concentration, and mood) due to an overwhelming sense of fatigue. She is a retired judge who still works part-time. Medical history is pertinent for hypertension, depression, postmenopausal status, and status post-tonsillectomy. She has a prior history of alcohol abuse (abstinent for over 20 years) and current tobacco use. Her physical examination is notable for a pleasant female with a BMI of 38 with mild micrognathia, a crowded, shallow oropharynx, and a neck circumference of 16 inches. The remainder of the medical and neurologic examination is unremarkable.

#### • What are the common etiologies of insomnia?

Insomnia is the most common sleep complaint in the industrialized world, with insomnia complaints found in 30% to 40% of the population. To be given a diagnosis of insomnia, the individual must complain of at least a 1-month duration of poor sleep quality or difficulty with sleep initiation or maintenance that is associated with at least 1 of the daytime impairments listed in **Table 12**.<sup>17</sup> The sleep difficulty occurs despite adequate opportunity and circumstances for sleep. Although reports of episodic insomnia symptoms are high, only 8% to 19%

**Table 13.** Common Etiologies of Insomnia

Primary
Psychophysiologic insomnia
Paradoxical insomnia
Idiopathic insomnia
Secondary
Adjustment (acute social stressors such as bereavement)
Insomnia due to mental disorder (eg, depression)
Inadequate sleep hygiene
Behavioral insomnia of childhood
Insomnia due to drug or substance abuse
Insomnia due to medical conditions (eg, chronic pain)
Insomnia <i>not</i> due to substance or known physiologic condition
Physiologic insomnia
Insomnia secondary to another primary sleep disorder (eg, sleep disordered breathing, circadian rhythm disturbance, restless legs syndrome)

of the general population meet the diagnostic criteria for insomnia with the combination of complaints and significant distress and/or impairment.<sup>57</sup>

The ICSD-2 separates the etiologies for insomnia into primary and secondary classifications (**Table 13**). Diagnostic criteria for primary insomnia (3 defined types) are as follows: Psychophysiological insomnia is defined as a heightened level of arousal with learned sleep-preventing associations that result in a complaint of insomnia and associated decreased functioning during wakefulness. Paradoxical insomnia is defined as a severe insomnia that occurs without evidence of objective sleep disturbance and without daytime impairments to the extent that would be suggested by the amount of sleep disturbance reported. Idiopathic insomnia is a chronic condition, with onset during infancy or childhood; it has no identifiable precipitant or cause and has a persistent course with no periods of sustained remission. To be diagnosed with a form of primary insomnia, symptoms cannot be better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.<sup>17</sup>

- **Which sleep disorders must be considered as contributing to this patient's insomnia presentation?**

### RESTLESS LEGS SYNDROME

The patient clearly endorses the 4 essential components of the RLS diagnostic criteria: an urge or compulsion to move the legs, usually accompanied by uncomfortable or unpleasant sensations, primarily in the legs; the urge to move or uncomfortable sensations that begin or worsen during rest; symptoms (the urge to move or uncomfortable sensations) are partially or totally relieved

**Table 14.** Risk Factors for Sleep Apnea

Modifiable	Unmodifiable
Obesity	Gender
Alcohol	Postmenopausal status
Tobacco use	Genetics
Sedative use	Race/ethnicity
Sleep deprivation	Disorders with craniofacial abnormalities
Supine posture	Diabetes mellitus
Respiratory allergies	Chronic uremia
Nasal congestion	Dysautonomia

by movement (at least initially in presentation); and the urge to move or the uncomfortable sensations are worse in the evening or early part of the night compared to during the day. RLS is a common and often disabling sensorimotor disorder. Epidemiologic studies suggest that 7% to 10% of the general population in the United States and Northern Europe may have RLS symptoms,<sup>58-61</sup> and 2% to 3% have symptoms frequent and severe enough to warrant medical attention.<sup>62,63</sup> Medically significant RLS occurs in approximately 0.5% of children aged 8 to 11 years and in 1% of those aged 12 to 17 years.<sup>64</sup> RLS is 1.5 to 2 times more common in adult women than men, but there is no significant gender difference in prevalence for children or adults younger than age 30 years.<sup>63,64</sup> RLS prevalence and disease severity increase with age.<sup>65</sup>

Paresthesias often accompany the urge to move, with the legs being primarily affected. As the disease progresses, other body parts (shoulders, arms, and trunk) may also be affected.<sup>66,67</sup> When the patient is at rest, the urge to move increases in a crescendo pattern until the patient moves his or her leg. When the patient attempts to suppress the urge, a “build-up” phenomenon may occur and the limb may jerk involuntarily.<sup>66</sup> The circadian pattern of the symptom complex often results in significant sleep loss and disruption.<sup>68</sup> Although not required to establish the diagnosis, a PSG reveals PLMS in approximately 80% to 90% of all RLS patients.<sup>65</sup> PLMS have high sensitivity for RLS but are associated with several other conditions and therefore have low specificity (Table 9). Additional information supportive of the diagnosis of RLS includes a positive family history and/or a history of iron deficiency anemia.

### SLEEP-DISORDERED BREATHING

The case patient has several risk factors for sleep apnea (**Table 14**). She is obese (BMI of 38), and obesity is the most common risk factor for sleep apnea, specifically central obesity. Sleep apnea is more prevalent with increasing age,<sup>69</sup> reaching peak prevalence rates in patients between 65 and 75 years of age.<sup>70</sup> Men appear to have a

**Table 15.** Treatment Strategy for Restless Legs Syndrome

Symptom Description	Option 1	Option 2	Option 3
Daily*	Dopamine agonist	Opioids	Select anti-epileptic drugs (eg, alpha-2-delta types: pregabalin and gabapentin) Levodopa
Frequent but at night only	Benzodiazepines/benzodiazepine receptor agonists	Opioids	
Occasional	Levodopa	Benzodiazepines/benzodiazepine receptor agonists	Opioids
Painful	Antiepileptic drugs, opiates	Dopamine agonist	Benzodiazepines/benzodiazepine receptor agonists
All patients with serum ferritin < 50 µg/L (treatment concurrent with other medical treatment)	Oral iron (ferrous sulfate) + 200 mg vitamin C 1–3 times daily as tolerated; follow with regular tests for indications of hemochromatosis	If clearly iron deficient (ferritin < 18 µg/L) and not responding to oral iron, consider referral for intravenous iron treatment	

Adapted with permission from Earley CJ. Clinical practice. Restless legs syndrome. *N Engl J Med* 2003;348:2105.


\*Daily symptoms refer to those occurring ≥ 3 per week. Frequent symptoms occur 1 to 3 times per week. Occasional symptoms occur fewer than once per week on average.

higher rate of sleep apnea than do women, with a ratio of 2:1 to 10:1, depending on the study.<sup>70</sup> However, the prevalence of sleep apnea in women begins to approach that of men once a woman reaches menopause.<sup>71</sup> Insomnia can often be the primary presenting complaint in women with apnea.<sup>24</sup> Any condition or anatomic abnormality that narrows the posterior airspace can predispose to the development of sleep apnea. This includes nasal obstruction, retrognathia or micrognathia, tonsillar hypertrophy, and macroglossia. Several studies have demonstrated that patients with a family history of sleep apnea have a higher risk for developing the condition themselves.<sup>72</sup> Use of alcohol or sedatives may contribute to the development or worsening of sleep apnea.<sup>73</sup> A longitudinal epidemiologic study showed that smokers are at an increased risk for developing sleep apnea. Hypothyroidism can also contribute to the development of sleep apnea by causing macroglossia or obesity. Other conditions such as acromegaly, amyloidosis, vocal cord paralysis, post-polio syndrome, neuromuscular disorders, Marfan syndrome, and Down syndrome are also associated with sleep apnea.<sup>70</sup>

SDB is diagnosed with either inpatient monitored PSG or, more recently, the use of an ambulatory apnea monitoring device under specific clinical conditions.<sup>74</sup> SDB occurs when abnormal breathing patterns disrupt sleep. There are different types, which can occur in one of several patterns. An apnea is defined as the cessation of airflow for at least 10 seconds. Hypopnea is defined as an event lasting at least 10 seconds with a greater than 30% reduction in movement or airflow and with at least a 4% oxygen desaturation. Significant cardiovascular comorbidity has been detected at an apnea-hypopnea index (AHI) of 5 events or more per hour. When respiratory effort occurs in the context of these events, it is defined as an obstructive event, whereas when the

abdominal and thorax pressure belts demonstrate no effort, the event is considered to be central in origin. Events that begin as central events but end with the patient demonstrating effort are labeled mixed events.<sup>18</sup>

#### SLEEP STUDY RESULTS

 The case patient undergoes an inpatient PSG, which reveals obstructive sleep apnea with a SDB index of 35, often associated with arousals and leg kicks.

#### • What are management options for this patient?

Treatment for RLS should be individualized with consideration of the patient's specific clinical presentation and associated conditions. Treatment strategies usually include a combination of aggravator reduction (eg, avoiding medications and other substances known to aggravate symptoms, including alcohol, nicotine, selective serotonin reuptake inhibitors, dopamine antagonists, antihistamines) along with behavioral and pharmacologic therapy (**Table 15**). Dopamine agonists demonstrate the highest clinical efficacy; however, several other medications have also proven efficacious for symptomatic relief, including specific anti-epileptic medications, opioids, and benzodiazepines.<sup>75</sup> Treatment strategies should be based on iron status, disease severity, frequency/duration of symptoms, time of onset of bothersome symptoms, presence of pain, and drug side effects (**Table 15**).<sup>75</sup> RLS is closely tied to iron status, and all patients should be screened and treated for iron deficiency. Although iron deficiency has been defined as a ferritin level of 18 µg/L or a transferrin saturation percentage of 16, for RLS, ferritin levels less than 50 µg/L have been correlated with increased symptom severity, decreased sleep efficiency, and increased PLMS associated with arousal.<sup>76</sup>

Treatment for patients with sleep apnea is aimed at reducing morbidity and mortality and improving quality of life, which can be accomplished by preventing the cardiovascular consequences of sleep apnea and reducing the complications of EDS. Because of the correlation between sleep apnea and obesity, particularly increased upper body mass, obese patients should be encouraged to lose weight. Exercise and fitness should be recommended to all patients, both to improve sleep apnea and reduce cardiovascular disease risk. Eliminating alcohol intake close to bedtime is also important. Lying in the supine position results in a decrease in the size of the pharynx because of the effects of gravity, which may cause positional sleep apnea in some patients.<sup>77,78</sup> These patients may benefit from sleep-position training designed to prevent sleeping in the supine position.<sup>79</sup> The most common medical treatment is positive airway pressure (continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]), which is used to keep the airway from collapsing. A variety of oral appliances have also been developed that mechanically hold the airway open, preventing collapse. Surgical intervention is also an option primarily in those with snoring or mild sleep apnea. The aim of surgery is to open the airway sufficiently to eliminate or to reduce obstructions to a clinically insignificant level. Surgical management in adults often involves reconstruction of the soft tissues (such as the uvula and the palate) or the bony tissues (the jaw).

#### **PATIENT FOLLOW-UP**



The patient is successfully managed with CPAP therapy for sleep apnea and pramipexole at a maximum dose of 0.25 mg daily for RLS. The patient does well on this therapy, but after 7 years her RLS symptoms start to become more intense, occurring in both the arms and legs over the course of an entire day. Her neurologist recommends increasing the pramipexole dose to 1 mg daily. After being on this dosage for 1 year without much improvement, she is referred to a sleep specialist for a second opinion. She also reports for the first time that over the course of the past year she has been experiencing a conscious compulsion for nocturnal eating, leading to a 9-lb weight gain, and she has engaged in compulsive spending sprees.

- **What conditions is this patient suffering from?**

#### **RLS AUGMENTATION**

RLS augmentation was first described in 1996 in an uncontrolled study of 30 RLS patients treated with dopaminergic medications.<sup>80</sup> Augmentation was characterized by an earlier onset of symptoms, a decreased la-

tency of the onset of symptoms during rest, progression of symptoms to involve the upper extremities and trunk, an increase in symptom intensity, and a diminishing effect of the medication. It occurs in 70% to 80% of RLS patients treated with levodopa.<sup>80</sup> Two dopaminergic agents are approved (pramipexole and ropinirole) to treat RLS and have been shown to be a better treatment option than levodopa because of their longer half-life and reduced potential for augmentation.<sup>81-83</sup> Augmentation from dopaminergic agents tends to occur less frequently than augmentation from levodopa, with a reported prevalence of approximately 20% over the first 2 years of medication use. However, it may occur more frequently with longer term use.<sup>81,82,84</sup> The clinical features of augmentation caused by dopaminergic agents can be differentiated from RLS itself.<sup>85</sup> The basic feature of augmentation is a worsening of RLS severity while the patient is on dopaminergic agents.<sup>86</sup> Augmentation may be associated with diminishing or blurring of the RLS diagnostic criteria originally satisfied by the patient before treatment. Symptoms will begin to encompass new areas of the body, including the arms and trunk. On occasion, the circadian pattern of symptoms may no longer be present, and symptoms may begin earlier in the day. Some patients may even report that they obtain much less relief of their RLS symptoms with movement or walking than they previously had.

Early morning rebound (EMR) is another complication of dopaminergic agents that is characterized by recurrence of RLS symptoms in the early morning. EMR is observed in 20% to 35% of patients taking levodopa and is usually of lesser clinical significance for the patient than augmentation.<sup>85</sup> Treating physicians must be aware of EMR and how to differentiate it from augmentation since treatment may vary. Rebound is considered an end-of-the-dose effect. EMR occurs only with short-acting drugs such as levodopa and does not generally cause an increase in the RLS intensity. It also does not extend to other parts of the body, unlike augmentation.

#### **DOPAMINE DYSREGULATION SYNDROME**

Compulsive behaviors, including change in appetite, punding (compulsive collecting of things), gambling, shopping, hypersexuality, and stealing are key features of dopamine dysregulation syndrome (DDS).<sup>87</sup> DDS is a neuropsychological behavioral disorder associated with substance misuse and addiction that was initially recognized in individuals treated for Parkinson's disease (PD) with dopamine replacement therapy.<sup>87</sup> DDS affects approximately 4% of PD patients, who are often susceptible males with early-onset PD. The patients and family members of those with DDS often suffer significant social

**Table 16.** Primary Parasomnias Categorized by Phase of Sleep in Which It Occurs

Non-REM Sleep	REM Sleep	Any Sleep Stage
Confusional arousals	REM behavior sleep disorder	Nocturnal groaning
Sleep walking		Bruxism
Sleep terrors	REM-related painful erections	Enuresis
Sexsomnias		Rhythmic movement disorders
Sleep-related eating disorder	Dream anxiety attacks, nightmares	Somniloquy
	Recurrent sleep paralysis	

REM = rapid eye movement.

consequences due to the extreme behaviors exhibited by patients. There have been several recent reports of DDS cases occurring in RLS patients treated with dopamine replacement therapy.<sup>85,88,89</sup> While DDS has been associated with the pathologies of PD and more specifically with impaired cognition involving executive function, the cognitive deficits demonstrated in RLS patients have been associated primarily with the accompanied sleep loss and not with the underlying disease pathology.<sup>68,90</sup> This patient had been sleeping well on medication prior to the onset of the changes in behavior and had no indication of a loss of cognitive function, as has been reported for PD patients with DDS. In the reported cases of DDS in RLS patients treated with dopamine replacement therapy, compulsive behaviors resolved almost immediately when the medication was stopped.<sup>89</sup>

It is important to distinguish the current case of compulsive eating due to DDS from sleep-related eating disorder (SRED) and nocturnal eating syndrome (NES), which combine features of sleep disorders and eating disorders. These syndromes are types of parasomnias characterized by compulsive eating at night, poor sleep quality, and morning anorexia. Parasomnias are defined as unpleasant or undesirable behavioral or experiential phenomena that occur predominantly or exclusively during the sleep period. A waking-dissociated state is likely the basis for many parasomnias (both REM and non-REM), which may be categorized as primary parasomnias or secondary parasomnias (Table 16).<sup>17</sup> The primary sleep parasomnias can be classified according to the sleep state of origin: REM sleep, non-REM sleep, or miscellaneous (ie, those not respecting sleep state). SRED occurs with partial arousal, whereas NES occurs with maintenance of full awareness.<sup>91</sup> Other parasomnias may be common in the general population, and while they sometimes can be frightening to patients and family members, most are benign and do not warrant pharmacotherapy. However, the neurodegenerative disorders (particularly alpha synucleinopathies and more recently

tauopathies) are associated with REM sleep behavior disorder, which usually responds well to clonazepam. It is important to remember that nocturnal seizures are in the differential diagnosis for parasomnias and vice versa. Additional electroencephalography channels with video monitoring together with a thorough history looking for features of seizure such as rhythmic jerking, tongue-biting, and or bowel/bladder incontinence are key to differentiating the possible diagnoses.


• **What is the approach to managing the patient with RLS augmentation and/or DDS?**

Evaluation for augmentation should be focused on the history and any pertinent findings from the initial work-up that are consistent with the criteria for augmentation. Iron deficiency anemia, other medical conditions, and the effects of medications may exacerbate or resemble augmentation. It would be beneficial to recheck iron studies, to review medication lists for agents that may aggravate RLS, and to review the patient's medical history. Few studies have investigated the treatment of augmentation. Prevention of augmentation is a major goal in treating patients with RLS. Physicians should try to maintain the lowest possible dose of dopaminergic agents,<sup>85,92-94</sup> and the maximum dosage used in clinical trials should be followed closely. Nevertheless, maintaining the dose within the recommended limits may still lead to augmentation.

Augmentation often warrants treatment changes that may further exacerbate symptoms during the washout period. As patients are tapered off the dopaminergic agent, they may experience withdrawal effects that usually consist of restlessness and discomfort, which may be quite severe. It is important to counsel the patient about this phenomenon as it is very common, especially when higher doses of these medications are used. Currently, there are no standard guidelines on how to taper patients off dopaminergic agents, so providers should manage patients on a case-by-case basis. It remains controversial whether levodopa or the dopaminergic agents should be stopped immediately or tapered slowly.<sup>95</sup> Opioids or certain anticonvulsants are usually the classes of choice when switching a patient to a new RLS regimen.<sup>95</sup> Along with medication changes, nonpharmacologic management and lifestyle modification should be considered, such as additional adjunct therapy including physical and mental activities, massages, hot baths, and avoiding potential aggravators.<sup>68</sup> Withdrawal of the dopamine agent usually results in almost immediate resolution of DDS symptoms. Interestingly, in some instances patients may have little insight into their compulsive behaviors until after the removal of the dopamine agent, which further underscores

the importance of preventative strategies to avoid these presentations when possible.<sup>89</sup>

#### PATIENT FOLLOW-UP

 This patient is advised to taper off the dopamine agonist, and gabapentin is initiated to treat her RLS. After just a few weeks of coming off the dopamine agonist, she notices significant improvement in her RLS symptoms and sleep quality. After 1 month, she has lost all of the associated weight. Moreover, she becomes aware of her change of behaviors while on this medication and notes complete resolution of her “compulsive behaviors.”

#### CONCLUSION

Between 50 and 70 million Americans suffer from sleep disorders annually. Sleep deprivation can have significant effects on overall cognition and mood. Untreated sleep disorders can negatively impact personal health as well as public health and safety. Neurologists frequently encounter patients with sleep disorders, not only because of the neurologic nature of the symptoms, but also because several neurologic disorders are associated with disordered sleep. As such, neurologists must have a sound understanding of basic sleep medicine, allowing them to adequately identify patients at risk for sleep disorders and subsequently direct them to appropriate evaluation and treatment.

#### BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to [www.turner-white.com](http://www.turner-white.com) and select Neurology from the drop-down menu of specialties.

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