Sleep-Related Movement Disorders

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Relationship Disclosure: Dr Silber reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Silber discusses the unlabeled use of gabapentin, pregabalin, opioids, and benzodiazepines for the treatment of restless legs syndrome.

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ABSTRACT

Purpose of Review: This article reviews the sleep-related movement disorders, including restless legs syndrome (RLS; Willis-Ekbom disease), periodic limb movement disorder, rhythmic movement disorders, sleep-related bruxism, and sleep-related leg cramps.

Recent Findings: The prevalence of clinically significant RLS is 1.5% to 3.0%. The pathophysiology of RLS may involve abnormal iron transport across the blood-brain barrier and down-regulation of putaminal D2 receptors. The availability of the rotigotine patch provides an additional form of dopaminergic therapy for RLS. Calcium channel alpha-2-delta ligands (gabapentin, gabapentin enacarbil, and pregabalin) provide alternative therapies for RLS especially in patients with augmentation, impulse control disorders, or hypersomnia induced by dopamine agonists. Long-term use of opioid medication is safe and effective for refractory cases of RLS.

Summary: RLS is a common disorder causing considerable morbidity. Accurate diagnosis and appropriate investigations are essential. Many effective therapies are available, but the side effects of each class of medication should be considered in determining optimal treatment. Periodic limb movements of sleep, bruxism, and rhythmic movement disorders are sleep-related phenomena often accompanying other sleep disorders and only sometimes requiring primary therapy. Sleep-related leg cramps are generally idiopathic. Management is challenging with few effective therapies.

Continuum (Minneap Minn) 2013;19(1):170–184.

INTRODUCTION

Movement disorders and sleep are intimately related. Some abnormal movements are at least partially suppressed by sleep, including tremor, chorea, dystonia, and tics, while others are activated by sleep, including periodic limb movements, rhythmic movement disorder, bruxism, and REM sleep behavior disorder. This article focuses on the sleep-related movement disorders as defined by the *International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*. Restless legs syndrome (RLS) will be emphasized, but periodic limb movement disorder, rhythmic movement disorder, sleep-related bruxism, and sleep-related leg cramps will also be addressed.

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RESTLESS LEGS SYNDROME

RLS, also known as Willis-Ekbom disease, was accurately described by Thomas Willis in 1685 but first delineated as a unique condition by Dr Karl-Axel Ekbom of Sweden in 1945 when he described a ''hitherto overlooked disease in the legs.''[1] Initially believed to be a rare condition, later studies suggested prevalence as high as 10% to 15%. However, recent large epidemiologic studies in Europe and the United Sates have determined that the true prevalence for RLS that causes moderate distress and occurs at least twice a week is in the range of 1.5% to 3.0%.[2,3] RLS is more common in women than in men. It can commence in childhood, when it is often diagnosed as ''growing

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TABLE 9-1 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Restless Legs Syndrome**[a]

- An urge to move the legs that is usually, but not always, accompanied or caused by uncomfortable and unpleasant leg sensations
- The symptoms begin or worsen during rest or inactivity
- The symptoms are partially or totally relieved by movements such as walking or stretching for at least as long as the activity continues
- The symptoms only occur or are worse in the evening or night than during the day
- The symptoms are not solely accounted for as being primary to another condition, such as leg cramps or positional discomfort

[a] Modified from American Academy of Sleep Disorders.[4] Used with permission of the American Academy of Sleep Medicine, Darien, IL, 2012.

pains.'' The incidence increases with age, and symptoms may progress with time; however, many patients experience unexplained remissions lasting at least a month.

Diagnosis of Restless Legs Syndrome

The diagnosis of RLS is made clinically. All five of the essential diagnostic features must be present (**Table 9-1**),[4] and care must be taken to exclude diagnostic mimickers (**Table 9-2**).[5] The essential features are an uncontrollable urge to move the legs while at rest (either sitting or lying down), with at least temporary relief obtained by movement such as walking. The symptoms only occur in the evening or night or are the worst at those times (**Supplemental Digital Content 9-1**, *links.lww.com/CONT/A20*). The urge to move is usually, but not always, associated with unpleasant leg sensations, variously described as creepy, crawly, tingly, or a deep ache. Many patients find it hard to describe the nature of the discomfort. RLS symptoms may alternate between legs and may be asymmetric. It is not unusual for patients with severe RLS to describe similar symptoms in the arms and occasionally the trunk. Later in the disease course, the relief by movement may be less evident but should have been present earlier.

In a study of 788 patients who endorsed the first four criteria on a questionnaire, 15% were found to have an alternative diagnosis after an interview with an expert.[6] Nocturnal leg cramps and positional discomfort were the most common mimickers, and when additional questions were added to rule out these complaints, the specificity of the questionnaire rose to 94%.[7] Patients describe leg cramps as hardening of a muscle group, often gastrocnemius-soleus,

TABLE 9-2 **Diagnostic Mimickers of Restless Legs Syndrome in Approximate Decreasing Order of Importance**

- Leg cramps
- Positional discomfort
- Habitual foot tapping
- Fibromyalgia
- Arthritis
- Venous stasis
- Leg edema
- Painful peripheral neuropathy
- Painful legs and moving toes syndrome

KEY POINTS

- Restless legs syndrome that is prominent enough to occur at least twice a week and cause moderate or severe distress has a prevalence of 1.5% to 3.0%.
- Restless legs syndrome is diagnosed clinically and requires a history of an uncontrollable urge to move the legs while at rest that is worse in the evening or night and is relieved by movement such as walking.
- Mimickers of restless legs syndrome, especially sleep-related leg cramps relieved by stretching or massaging the affected muscle and positional discomfort relieved by changing position rather than walking, must be excluded.

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KEY POINTS

- More than 50% of patients with restless legs syndrome have a family history of the disorder that is usually inherited in an autosomal dominant pattern. Multiple loci and several polymorphisms associated with restless legs syndrome have been identified.
- Low intracerebral iron, especially in the basal ganglia, possibly related to abnormalities in iron transport across the blood-brain barrier, may underlie restless legs syndrome. Restless legs syndrome is also associated with abnormalities in the dopamine system, possibly due to down-regulation of D2 receptors.

with intense pain relieved not by walking but by massaging the muscle or standing on the toes. Positional discomfort, such as paresthesia or pain in a leg, is relieved by changing position in bed, which alone does not help RLS. Habitual foot tapping during wakefulness or drowsiness is a learned behavior not associated with an urge to move and can easily be discontinued when attention is drawn to the activity. Discomfort from venous stasis, edema, peripheral neuropathy, or arthritis may need to be considered. Fibromyalgia or nonspecific myofascial leg pain may be worse at night, but the characteristics rarely fulfill all five RLS diagnostic criteria.

Etiology and Pathophysiology of Restless Legs Syndrome

What causes RLS? Increasing evidence exists to suggest an underlying genetic basis for the disorder. Over 50% of patients have a family history of RLS in first-degree relatives, sometimes in three or more generations. Inheritance is usually autosomal dominant. Linkage studies have identified multiple loci on different chromosomes associated with RLS in North American, French Canadian, and Italian populations. Genomewide association studies have found several predisposing polymorphisms in a variety of genes. The most frequently reported in multiple populations is BTBD9 on chromosome 6p with a protein product widely expressed in the brain.[8]

Other clues to understanding RLS involve disturbances in iron and dopamine function. A link between RLS and iron deficiency was recognized by Dr Ekbom, and studies have confirmed that low systemic iron stores are associated with increased RLS severity. Researchers and clinicians have shown considerable interest in the possibility that RLS may be a disorder characterized by low intracerebral iron.[9,10] CSF ferritin levels are lower in patients with RLS than in controls even in the absence of systemic iron deficiency. MRI and transcranial sonography have shown reduced iron stores in the basal ganglia, and autopsy studies have demonstrated decreased substantia nigra iron, ferritin, and transferrin receptor concentrations with increased transferrin, a pattern suggestive of low iron stores. Abnormalities in the transport of iron across the blood-brain barrier in RLS may be the underlying mechanism.[11]

The excellent response of RLS to dopaminergic medications and the exacerbation of RLS with dopamine antagonists suggest that dopamine deficiency may be at the heart of the disorder. RLS is associated with down-regulation of dopamine D2 receptors in the putamen, and the degree of loss of receptors in RLS correlates with severity of the disorder.[12] The levels of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis, are increased in the substantia nigra in RLS, presumably as a compensatory mechanism to reduced dopamine receptors. Similar findings of reduced putaminal D2 receptors are seen in iron deficiency in rats along with increased tyrosine hydroxylase levels in the brain.[12] These findings suggest a possible link between intracerebral iron deficiency and RLS.

Secondary causes of RLS include acquired iron deficiency, chronic renal failure, peripheral neuropathy, and certain medications. These medications include most antidepressants (with the probable exception of bupropion), dopamine antagonists (neuroleptic agents used to treat psychoses and antinausea medications), and possibly antihistamines. RLS is often precipitated or exacerbated by pregnancy.

Consequences of Restless Legs Syndrome

The clinical consequences of RLS can be severe.[13] Quality-of-life studies have

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consistently demonstrated low questionnaire scores for patients with moderate to severe disease, equivalent to those seen with other chronic diseases, such as osteoarthritis, rheumatoid arthritis, diabetes mellitus, and cardiac failure. Sleep-onset insomnia and sleep-maintenance insomnia are reported by 50% to 85% of patients, which results in many hours awake each night. Studies have shown an increased prevalence of depression and anxiety in patients with RLS compared to controls. Recently, a possible relationship between RLS and vascular disease has been hypothesized.[14] Many of the cross-sectional studies performed have methodologic flaws, and the few prospective studies are contradictory; some, but not all, suggest a higher incidence of vascular disease after diagnosis of RLS or periodic limb movements of sleep, but with low odds ratios. Proposed mechanisms for such a relationship include the effects of sleep deprivation and arousals from periodic limb movements causing excessive sympathetic stimulation. Because of the uncertainty of the findings, the relatively low increased risk, and the lack of interventional studies, current therapeutic decisions should not be made based on concern about vascular risk.

Investigation and Management of Restless Legs Syndrome

The diagnosis of RLS is made clinically on history. Polysomnography (PSG) is not routinely indicated unless an additional sleep disorder such as obstructive sleep apnea is suspected. Although 85% of patients with RLS will have periodic limb movements of sleep on PSG,[15] such a finding is nonspecific, especially in older people. Secondary causes of RLS should be considered. A history of menorrhagia, gastrointestinal hemorrhage, anemia, or frequent blood donation should prompt measurement of iron stores. Symptoms and signs of a possible peripheral neuropathy should be elicited. Medications that can cause or exacerbate RLS should be noted, and the temporal relationship between the onset of RLS and their use determined. Serum ferritin concentration is the most sensitive measure of iron stores and should be measured in patients with chronic RLS. Serum ferritin is an acute-phase reactant, and therefore concentrations may be spuriously high in the setting of acute or chronic inflammatory disorders. Under those circumstances, total iron-binding capacity and percent saturation should also be measured. Nonpharmacologic approaches and a number of classes of drugs are available for the treatment of RLS (**Table 9-3**).

Nonpharmacologic management. If the serum ferritin concentration is below the lower limit of normal for age, sex, and the specific laboratory, then a cause should be sought and iron supplementation prescribed. If the level is between the lower level of normal and 50 μg/L, then iron therapy can be considered, especially in patients who prefer natural therapies or appear resistant to drug treatment, as several studies have shown that levels <50 μg/L correlate with RLS severity. Many iron preparations, such as ferrous sulfate or ferrous gluconate, are available. Iron should be administered apart from food, generally in two doses, with a total daily amount of elemental iron of 150 mg to 200 mg. Vitamin C (200 mg) should be added to each dose to enhance absorption. Serum ferritin concentration should be rechecked every 6 months. Open-label studies of IV iron dextran showed some promise, but two controlled trials using iron sucrose have been negative.[16,17] A recent small trial of ferric carboxymaltose (currently unavailable in the United States but under review by the US Food and Drug

KEY POINTS

- Restless legs syndrome has profound effects on quality of life, equivalent to those caused by other chronic medical illnesses, and is associated with insomnia, depression, and anxiety.
- An association may exist between restless legs syndrome and vascular disease, but more research is needed to better define the degree and nature of the relationship before basing therapeutic decisions on concern for vascular risk.
- Serum ferritin should be measured in patients with chronic persistent restless legs syndrome.
- Oral iron replacement should be administered with vitamin C if serum ferritin levels are abnormally low and should be considered if levels are low normal (<50 μ/L).

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TABLE 9-3 Selected Medications for Management of Restless Legs Syndrome

Drug and Type	Indications	Daily Dosage (mg)	Side Effects
Dopaminergic agents			
Pramipexole	Chronic-persistent restless legs syndrome (RLS)[a]	0.125–0.75	Nausea, augmentation, impulse control disorders, hypersomnia
Ropinirole	Chronic-persistent RLS[a]	0.25–4	Nausea, augmentation, impulse control disorders, hypersomnia
Rotigotine patch	Chronic-persistent RLS[a]	1–3	Nausea, augmentation, impulse control disorders, hypersomnia, patch-related skin reactions
Carbidopa/levodopa	Intermittent RLS	25/100	Nausea, lightheadedness, augmentation
Calcium channel alpha-2-delta ligands			
Gabapentin	Chronic-persistent RLS	600–2400	Hypersomnia, dizziness, unsteadiness, weight gain
Gabapentin enacarbil	Chronic-persistent RLS[a]	600	Hypersomnia, dizziness, unsteadiness, weight gain
Pregabalin	Chronic-persistent RLS	100–300	Hypersomnia, dizziness, unsteadiness, weight gain
Benzodiazepines			
Clonazepam	Intermittent or refractory RLS	0.25–1	Hypersomnia, unsteadiness, cognitive dysfunction
Temazepam	Intermittent or refractory RLS	7.5–30	Hypersomnia, unsteadiness, cognitive dysfunction
Zolpidem	Intermittent or refractory RLS	5–10	Amnestic reactions, sleepwalking or sleep eating
Opioids			
Codeine	Intermittent RLS	15–60	Nausea, constipation
Tramadol	Intermittent RLS	25–100	Nausea, constipation, augmentation, seizures
Oxycodone	Refractory RLS	10–20	Nausea, constipation, hypersomnia, cognitive dysfunction, unsteadiness, itch, sleep apnea
Methadone	Refractory RLS	5–15	Nausea, constipation, hypersomnia, cognitive dysfunction, unsteadiness, itch, sleep apnea

[a] US Food and Drug Administration-approved for RLS.

Administration [FDA]) showed modest but significant benefit in reducing RLS severity.[18] At present IV iron therapy should be restricted to patients with low iron stores and either a malabsorption state or complete intolerance to oral iron preparations. Iron gluconate or iron sucrose should be used, as iron dextran carries a risk of anaphylactic reactions.

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Other preventive nonpharmacologic approaches that can be considered include practicing regular moderate exercise; reducing caffeine, alcohol, or nicotine use; and considering withdrawal of predisposing medications. For management of the symptoms, techniques such as walking, bicycling, massaging, or soaking the affected limbs, or practicing mind-alerting techniques (eg, working on a computer or doing a crossword puzzle) can be helpful. Useful patient information can be found on the websites of the RLS Foundation (*rls.org*), the American Academy of Sleep Medicine (*yoursleep.aasmnet.org*), and the American Academy of Neurology's patient magazine *NeurologyNow* (*neurologynow.com*).

Dopaminergic agents. The nonergot dopaminergic agonists pramipexole, ropinirole, and rotigotine are approved by the FDA for the treatment of RLS. Extensive controlled trials have demonstrated their effectiveness. It is important to understand that the milligram equivalents of pramipexole and ropinirole are different: ropinirole doses should be approximately 4 times higher than those of pramipexole. Doses used are considerably lower than those used in Parkinson disease (maximum approved doses for RLS are 0.75 mg for pramipexole and 4 mg for ropinirole). Generally treatment should be started with 0.125 mg pramipexole or 0.25 mg to 0.5 mg ropinirole about 2 hours before symptoms start and increased every few days until relief is obtained. Some patients will require a dose of medication in the afternoon as well as the evening. Rotigotine is supplied as a once daily transdermal patch with doses of 1 mg to 3 mg. Lightheadedness, nausea, nasal congestion, and leg edema may occur with any dopamine agonist, and rotigotine may result in skin irritation under the patch. However, long-term use of these drugs is often limited by more serious side effects, such as augmentation, impulse control disorders, and daytime sleepiness.

Augmentation, as illustrated by **Case 9-1**, is the development of worsening RLS progressively earlier in the day after administration of dopaminergic medication in the afternoon or evening.[19] It may take the form of earlier onset of symptoms, worsening of preexisting symptoms, or spread of symptoms to the arms. In one study, augmentation developed in at least 42% of patients treated with pramipexole who were followed for a median of 9.7 years,[20] and other studies have shown similar frequencies.[21] Initially augmentation from dopamine agonists can be managed by adding a supplementary dose of medication earlier in the day, but in many patients worsening augmentation will eventually develop, necessitating discontinuation of the drug.

Impulse control disorders (ICD) include pathologic gambling, compulsive shopping, and hypersexuality. A case-control study showed a frequency of 17% in patients with RLS treated with dopamine agonists,[22] whereas other studies have shown frequencies between 6% and 12%.[23–25] Serious financial, social, and legal consequences of these disorders can occur. All patients treated with these agents should be warned of their risks, and these warnings should be repeated at each subsequent visit as the mean time from starting the medication to onset of an ICD is 9 months.[22] In almost every case, however, the ICD resolves promptly after discontinuing the drug. Excessive daytime sleepiness develops in about 50% of patients, and sleep attacks have been reported in about 10%, especially when taking higher doses.[20]

Levodopa in combination with a dopa decarboxylase inhibitor such as carbidopa is very effective in relieving RLS; however, an augmentation rate of up to

KEY POINTS

- Nonergot dopamine agonists (ropinirole, pramipexole, and rotigotine transdermal patch) are highly effective treatments for restless legs syndrome but are associated with augmentation (worsening of restless legs syndrome earlier in the day), impulse control disorders, and hypersomnia.
- Impulse control disorders, including pathologic gambling and compulsive shopping, occur in 6% to 17% of patients taking dopamine agonists for restless legs syndrome and may only manifest 9 months or longer after starting treatment.

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KEY POINT

- Calcium channel alpha-2-delta ligands (gabapentin, pregabalin, and gabapentin enacarbil) are all effective in restless legs syndrome but can cause dizziness, unsteadiness, hypersomnia, and weight gain.

Case 9-1

A 45-year-old woman had restless legs syndrome (RLS) for 6 years. At the time of first presentation her symptoms were present nightly, delaying sleep onset by 1 to 2 hours. Serum ferritin was 65 μg/L. She was prescribed pramipexole, which relieved restless legs at a dose of 0.5 mg taken at 8:00 PM. About a year later, RLS recurred in the evening after 7:00 PM, and an additional 0.25 mg pramipexole was prescribed at 6:00 PM. Over the next 5 years, RLS began intruding daily from 1:00 PM onward whenever she sat down, and over the past 6 months also began waking her at 1:00 AM. Restlessness developed in her arms at the same time as her legs. Her dose of pramipexole had been increased to 0.5 mg 4 times a day at noon, 6:00 PM, 8:00 PM, and 11:00 PM. She became excessively sleepy in the afternoon and evening, dozing while driving home from work and while watching TV or talking to her husband after dinner. Pregabalin was added in increasing doses, and pramipexole was withdrawn over a week. Initially her symptoms worsened during the transition, but within 2 weeks they had all resolved on a pregabalin dose of 100 mg 3 times a day. Her sleepiness improved.

Comment. This patient's history illustrates some of the difficulties using long-term dopamine agonists. The patient developed typical augmentation with the symptoms moving earlier in the day and spreading to the arms. As more frequent doses of medication were added progressively earlier in the day, her symptoms worsened, and she developed daytime sleepiness. Under these circumstances, the dopamine agonist medication should be slowly withdrawn, and a calcium channel alpha-2-delta ligand, such as gabapentin, gabapentin enacarbil, or pregabalin, substituted. If these are ineffective, an opioid may be needed.

80%[26] limits its use, and it should only be prescribed for occasional use with intermittent RLS.

Calcium channel alpha-2-delta ligands. The drugs gabapentin,[27] pregabalin,[28] and gabapentin enacarbil (a gabapentin prodrug) have all been shown to be effective in the management of RLS,[29] but only gabapentin enacarbil has been approved by the FDA for this purpose. The mechanism of action in RLS has not been clearly established. The mean effective total daily dose of gabapentin is 1800 mg and pregabalin 300 mg. Doses should be slowly increased based on effectiveness and patient tolerance. They can be administered 1 to 3 times a day, depending on the time of RLS symptoms. Gabapentin enacarbil is administered in a dose of 600 mg once daily in the late afternoon. Class side effects include hypersomnia, dizziness, unsteadiness, weight gain, and edema. Augmentation has not been reported.

Opioids. Opioid medication is highly effective in RLS. Low- to intermediate-potency drugs, such as codeine, may be useful in intermittent RLS, whereas high-potency agents may be needed in RLS refractory to other medications. Oxycodone, hydrocodone, and methadone have been used successfully. Tramadol is the only opioid agent in which augmentation has been reported, and it carries a slight risk of seizures. A long-term follow-up study of 76 patients using methadone for RLS showed a discontinuation rate of 15% in the first year and then continued efficacy without development of tolerance for the remainder over 10 years.[21] Usual doses needed are approximately 10 mg to 20 mg for oxycodone and 5 mg to

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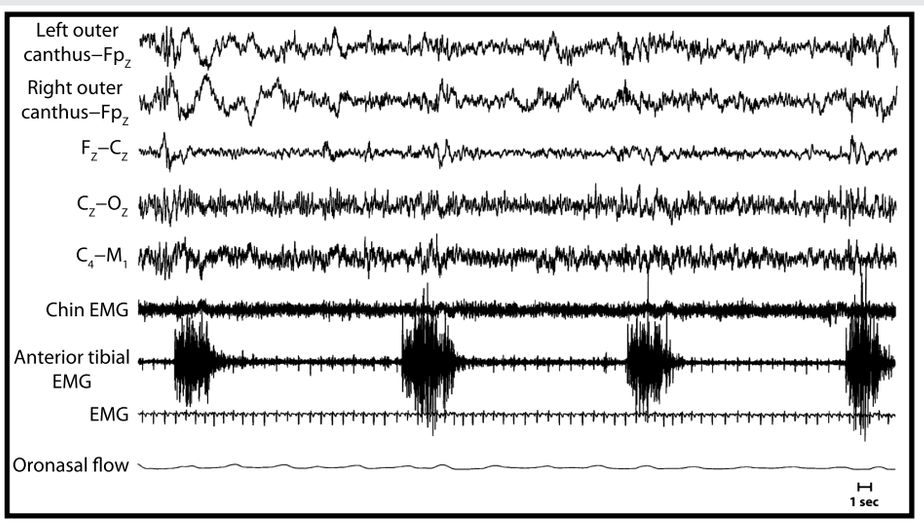

FIGURE 9-1 A 60-second polysomnography fragment showing four periodic limb movements of sleep associated with arousals.

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KEY POINT

- High-potency opioids, such as oxycodone, hydrocodone, and methadone, are highly effective for refractory restless legs syndrome but are addictive and may exacerbate sleep apnea. In most patients they can be used for prolonged periods with no tolerance and continued effectiveness.

15 mg for methadone. Side effects include itch (due to mast cell degranulation and not allergy), nausea, constipation, sleepiness, cognitive impairment, and gait unsteadiness. Obstructive sleep apnea can be exacerbated, and central sleep apnea can develop. The risk of dependance must be considered.

Benzodiazepines and benzodiazepine agonists. Clonazepam was among the earliest drugs reported to be successful in treating RLS; however, few clinical trials of benzodiazepine and benzodiazepine agonist agents have been conducted, and it seems likely they work by inducing sleep rather than by specifically targeting the symptoms of RLS. They may be helpful in patients with intermittent RLS at night, especially if insomnia disorder is also present, and they may be used to supplement other agents in refractory RLS. The longer-acting agents, such as clonazepam and temazepam, may induce sleepiness, unsteadiness at night in the elderly, cognitive symptoms, and potential dependance. The newer shorter-acting benzodiazepine agonists, such as zolpidem, may induce amnestic reactions and episodes of walking, eating, and occasionally driving while asleep.

Practical approach to treatment. A practical approach to RLS management is based on dividing the disorder into three categories: intermittent, chronic-persistent, and refractory. Intermittent RLS occurs less than twice a week, whereas chronic-persistent RLS occurs at least twice a week and causes sufficient distress to warrant daily preventive therapy. Refractory RLS is RLS treated with a dopamine agonist and an alpha-2-delta ligand with inadequate response or intolerable side effects.

Intermittent RLS can be treated with nonpharmacologic measures or intermittent use of levodopa, codeine, or a benzodiazepine. Chronic-persistent RLS should be treated with either a dopamine agonist or a calcium channel calcium channel alpha-2-delta ligand. If the drug chosen is ineffective or its use is limited by side effects, an agent of the other class should be tried. Iron status should be checked. For refractory RLS, other agents in the dopamine agonist or

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calcium channel alpha-2-delta agonist class can be considered, as well as the addition of a benzodiazepine at night; however, most patients at this stage of the disorder will require long-term opioid therapy.

PERIODIC LIMB MOVEMENT DISORDER

Periodic limb movements of sleep (PLMS), originally called nocturnal myoclonus, were first described almost 50 years ago. Bed partners notice rhythmic jerking of the legs during sleep with the sleeper generally unaware of the motor activity. Formal PSG criteria were first suggested in 1980 and have since been refined. A periodic limb movement (PLM) lasts 0.5 to 10 seconds with minimum amplitude of 8-μV increase in anterior tibial surface EMG voltage above the resting EMG.[4] At least four leg movements separated by 5 to 90 seconds between onsets of successive movements must occur in succession to be scored as PLMS (**Figure 9-1**).[30] Leg movements associated with arousals from respiratory events during sleep are excluded. PLMS occur more in the first half of the night than the second and usually do not persist into REM sleep.

The significance of PLMS has been debated ever since the movements were first identified. It is known that PLMS occur in 80% to 88% of patients with RLS,[15] but most patients with PLMS on a PSG do not have RLS. PLMS are common in patients with obstructive sleep apnea. They are found in 80% of patients with narcolepsy and 71% of patients with REM sleep behavior disorder.[15] They occur more frequently in Parkinson disease than in controls.[31] The prevalence of PLMS increases with

Case 9-2

A 54-year-old woman presented with problems sleeping during the past 3 years. She initiated sleep without difficulty at 11:00 PM but awoke 4 to 5 times during the night for uncertain reasons. Once awake she had difficulty returning to sleep, sometimes lying awake for up to an hour. During this time she thought about the next day's activities and worried about not being able to sleep. She woke with an alarm at 6:45 AM feeling unrefreshed. Her husband described regular leg kicking throughout the night without arm movements or vocalization, but she was unaware of the movements. She denied any discomfort in her legs or any urge to move while lying in bed or sitting in a chair. During the day she felt fatigued but did not fall asleep inappropriately. She denied symptoms of depression but felt mildly anxious. A polysomnogram showed a respiratory disturbance index of 4 per hour and a periodic limb movement index of 26 per hour, 14 of which were associated with arousals. Sleep efficiency was 69% because of 2 hours wake time after sleep onset. A diagnosis of psychophysiologic insomnia was made, and cognitive behavioral therapy for insomnia was instituted. Over the next few months her sleep maintenance problems markedly improved.

Comment. This case history illustrates how periodic limb movements of sleep are often an epiphenomenon related to other sleep disturbances rather than their cause. This patient did not have restless legs, and her primary complaint was remaining awake for prolonged periods during the night. Her symptoms responded to treatment for psychophysiologic insomnia. Institution of medication to treat her periodic limb movements would have been inappropriate.

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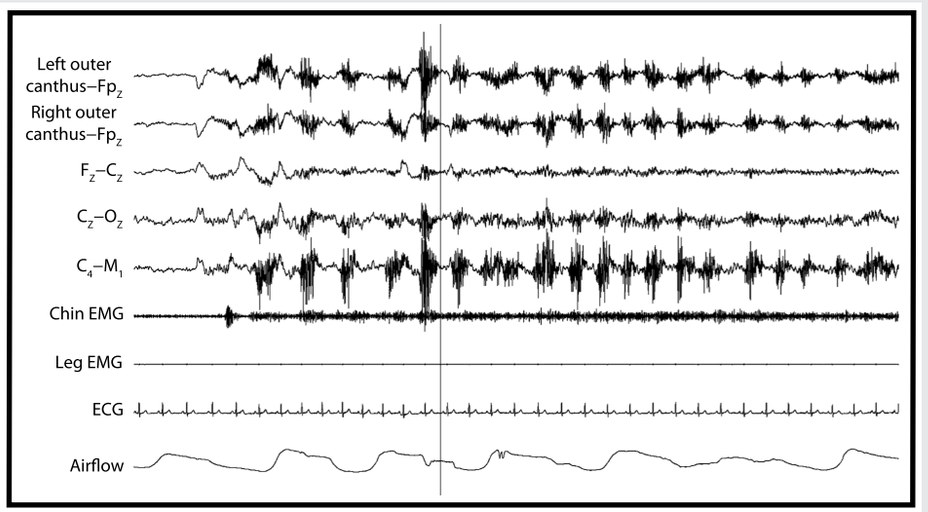

FIGURE 9-2 A 30-second polysomnography fragment showing typical EMG activity at about 1 Hz in the electrooculogram and EEG derivations typical of the masseter contractions of bruxism.

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KEY POINTS

- Periodic limb movements of sleep occur in 80% to 88% of patients with restless legs syndrome and are also frequent in narcolepsy, REM sleep behavior disorder, obstructive sleep apnea, and normal people 60 years of age or older.
- In the absence of restless legs syndrome, periodic limb movements of sleep are generally nonspecific epiphenomena that accompany fragmented sleep with arousals and only rarely require treatment as a specific disorder.

age. A study of 100 normal subjects found that no subjects aged below 30 years, 5.2% of subjects aged 30 to 49 years, and 29.0% of subjects aged more than 49 years had 30 or more PLMS over the course of a night.[32] Studies of community-dwelling subjects aged 60 years or older have found that 45% to 58% had five or more PLMS per hour.[33,34] The nonspecific nature of the movements, occurring in association with a wide range of other disorders as well as in normal older people, raises questions as to whether they have any clinical significance of their own or are simply an epiphenomenon of other disorders.

No definite relationship has been detected between the presence of PLMS and symptoms of insomnia or hypersomnia. Similarly, no association has been found between PLMS and PSG measures such as total sleep time, wake time after sleep onset, arousal index, and sleep efficiency.[35–37] In a study of 3916 EEG arousals associated with PLMS in 10 patients, the arousal occurred before the leg movement in 49.2%, simultaneous with the leg movement in 30.6%, and after the leg movement in 23.2%.[38] Treatment of PLMS with levodopa eliminates the movements, but the arousals persist.[39] Transient increases in heart rate and blood pressure[40–42] can occur in association with PLMS, even when unaccompanied by EEG arousals, but the changes in heart rate and blood pressure often precede the onset of the leg movement. These findings suggest that PLMS may be a response to nonspecific arousals rather than their cause. This is illustrated by **Case 9-2**.

As a result of these considerations, the entity of periodic limb movement disorder (PLMD), as opposed to the PSG finding of PLMS, is strictly defined.[4] In order for a diagnosis of PLMD to be made, PLMS must be present on PSG at a frequency of more than 5 per hour in children and more than 15 per hour in most adults. In addition, a clinical sleep disturbance or complaint of daytime fatigue attributable to PLMS must be present and not better explained by

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KEY POINT

- Sleep-related bruxism occurs in 8% of people, with highest prevalence in young adults. It can cause tooth damage and jaw discomfort but does not usually result in disrupted sleep.

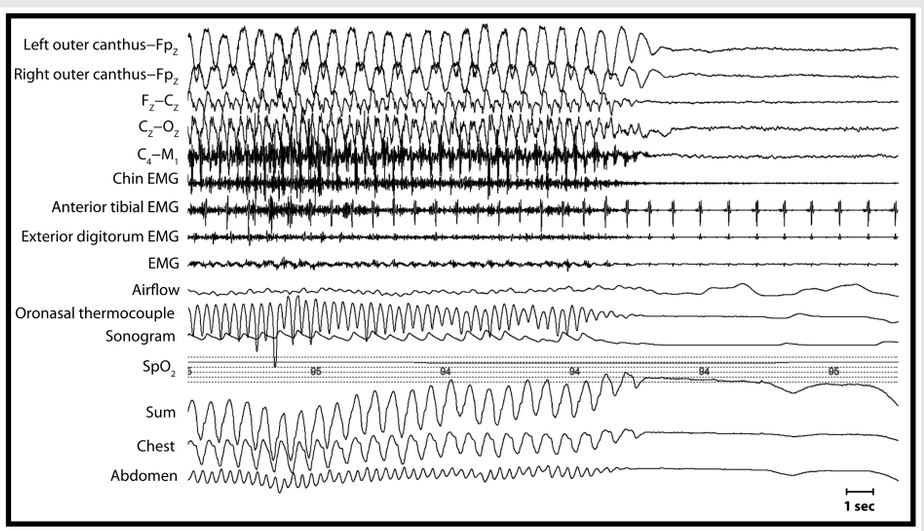

FIGURE 9-3 Polysomnography fragment showing the typical movement artifact in the EEG and respiratory channels at about 1.5 Hz typical of rhythmic movement disorder.
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any other current sleep, medical, neurologic, mental, or substance use disorder or the use of medications. A diagnosis of PLMD is thus not used for RLS with PLMS, and considerable caution should be exercised in diagnosing PLMD in the setting of sleep apnea or narcolepsy. When defined in this way, PLMD is a rare disorder.

The optimal treatment of PLMD is uncertain. Extrapolating from RLS, dopaminergic agonists may be the drugs of choice, and a sustained improvement in insomnia or hypersomnia with the use of dopaminergic agonists can help establish the correctness of the diagnosis. No controlled clinical trials of any agents for pure PLMD have been reported, however, beyond single night studies.

SLEEP-RELATED BRUXISM

In sleep-related bruxism (ie, tooth grinding or clenching), tonic contraction of the masseter muscles lasting at least 2 seconds, or trains of rhythmic masseter contraction at about 1 Hz are observed (**Figure 9-2**).[30] The PSG appearance is very typical, but audiovisual recordings are needed to definitively identify the phenomenon (**Supplemental Digital Content 9-2**, *links.lww.com/CONT/A21*). Bruxism is seen most frequently in light non-REM (NREM) sleep but may occur in any stage. It occurs in about 8% of people with prevalence highest in young adults and falling with age.[43] Consequences of bruxism must be present before it is considered a disorder. These include damage to the teeth, jaw discomfort, fatigue or pain or temporal headaches on wakening. Rarely masseter or temporalis muscle hypertrophy can ensue.

Apart from the physical effects described, there is little evidence for other adverse consequences of bruxism. PSG studies have not demonstrated any significant effects on total sleep time, wake time after sleep onset, sleep efficiency, sleep latency, or arousals. Subjectively, bruxism has been associated with perception of disrupted sleep, but the abnormal movements may be the result of sleep fragmentation rather than the cause. EEG alpha activity and

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heart rate increase before the onset of bruxism,[44] and the movements are frequently seen on PSG following arousals from obstructive apneas. Therapy generally involves the use of oral appliances to protect the teeth rather than medications aimed specifically at eliminating the jaw contractions.

RHYTHMIC MOVEMENT DISORDER

The movements of rhythmic movement disorder (RMD) consist of stereotyped contractions of large muscle groups at 0.5 Hz to 2 Hz during drowsiness or sleep[45] (**Figure 9-3**[30]; **Supplemental Digital Content 9-3**, *links.lww.com/CONT/A22*). They are most frequent in light NREM sleep but may sometimes be seen during REM sleep. The head or trunk may rock from side to side or back to front, and occasionally the legs may flex and extend. Subtypes, such as head banging (**Supplemental Digital Content 9-4**, *links.lww.com/CONT/A23*; **Supplemental Digital Content 9-5**, *links.lww.com/CONT/A24*) and body rocking (**Supplemental Digital Content 9-6**, *links.lww.com/CONT/A25*), have been named but no evidence exists to suggest that the different phenotypes have any specific significance. In order for the movements to be classified as a disorder, they must cause interference with normal sleep, impairment in daytime functioning, or bodily injury. RMD is common in infancy and early childhood (**Supplemental Digital Content 9-7**, *links.lww.com/CONT/A26*) but can persist into adulthood (**Supplemental Digital Content 9-8**, *links.lww.com/CONT/A27*). Intellectually handicapped children may be especially prone to injury from RMD.

The nature of RMD is controversial. Patients frequently explain that they have used the soothing and rhythmic nature of the movements to induce sleep from childhood, and often the movements start in drowsiness and then persist into light sleep. Patients with RMD often have sleep-onset insomnia, but it is not clear that sleep difficulties are induced by the movements rather than accompany them. Generally RMD only requires specific treatment if risk of bodily injury or severe disruption to the sleep of a bed partner exists, but insomnia may need to be independently managed. In young children, protective head gear or padding of cribs may prevent injuries from violent head movements. No clinical trials of medications for RMD have been reported, although the use of benzodiazepines such as clonazepam has been suggested.

SLEEP-RELATED LEG CRAMPS

Leg cramps are painful contractions of muscles of the leg or foot with resultant tightness or hardness. They occur most frequently at night, waking the patient from sleep. They are generally helped by stretching the affected muscle, often by standing. Most cramps are idiopathic, but they may occur in the setting of neuromuscular disorders such as radiculopathies, myopathies, ALS, and disorders of neuromuscular hyperexcitability such as Isaac syndrome. Hypocalcemia and other electrolyte disorders are rare causes. Nocturnal leg cramps are common and, when frequent, can result in sleep maintenance insomnia.

Treatment of leg cramps is difficult.[46] Quinine is probably effective, but the benefits are modest (about 20% to 25% reduction in number of cramps). It should not be used in most cases because the risk of severe side effects (including thrombocytopenia and cardiac arrhythmias) outweigh the potential benefits. Diltiazem may be effective, although supporting data are limited. No evidence indicates that magnesium is helpful. Anticonvulsants, such as gabapentin or levetiracetam, have not been adequately assessed.

KEY POINTS

- Rhythmic movement disorder, including head banging and body rocking, is common in infancy and early childhood but may persist into adulthood.
- Insomnia accompanying rhythmic movement disorder should be treated, but specific treatment for the movements is only needed if risk of bodily injury or severe disruption to sleep of a bed partner exists.
- Nocturnal leg cramps are usually idiopathic, and treatment is difficult; quinine should generally not be used because of serious potential side effects, including thrombocytopenia and cardiac arrhythmias.

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VIDEO LEGENDS

Supplemental Digital Content 9-1

Restless legs syndrome with obstructive sleep apnea. Video demonstrates restless legs syndrome (RLS) in a 72-year-old man. Note the severe kicking of the legs against one another. Polysomnography is not required for the diagnosis of RLS in adults but may be useful if other comorbidities are thought to exacerbate the condition. This patient presented with RLS symptoms and apneic spells and was subsequently diagnosed and treated for obstructive sleep apnea, which resulted in some improvement of his RLS symptoms. The patient's RLS symptoms did not respond to traditional first-line agents (dopamine agonists and gabapentin enacarbil) but responded well to opioid therapy, which resulted in some improvement.
links.lww.com/CONT/A20

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Supplemental Digital Content 9-2

Catathrenia and bruxism. Catathrenia (ie, sleep-related groaning) consists of sleep-related respiratory noises that occur predominantly during REM sleep. The typical respiratory noise in a patient with catathrenia has an expiratory quality and responds well to therapy with continuous positive airway pressure, which suggests that catathrenia may result from upper airway restriction. Between events, the patient in this video also exhibits bruxism (ie, grinding of the teeth), which is a movement disorder of sleep and may also represent an oral parafunctional activity.
links.lww.com/CONT/A21

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Supplemental Digital Content 9-3

Rhythmic movement disorder. Video demonstrates the often-stereotyped rhythmic movement of body rocking in a child. Body rocking tends to have a frequency of 1 Hz to 3 Hz and creates noise that sometimes awakens family members or bed partners.
links.lww.com/CONT/A22

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Supplemental Digital Content 9-4

Rhythmic movement disorder. Video demonstrates head banging in a child. Head banging consists of stereotyped and repetitive rhythmic movements of the head that occur during wake-to-sleep transitions and wakefulness.
links.lww.com/CONT/A23

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Supplemental Digital Content 9-5

Rhythmic movement disorder. Video demonstrates head banging in an adult.
links.lww.com/CONT/A24

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Supplemental Digital Content 9-6

Rhythmic movement disorder. Video demonstrates body rocking in an adult leading to 1 Hz to 2 Hz movement artifact in the polysomnogram. Body rocking is a sleep-related rhythmic movement disorder that interferes with normal sleep and can result in self-inflicted bodily injury.
links.lww.com/CONT/A25

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Supplemental Digital Content 9-7

Rhythmic movement disorder. Video demonstrates rhythmic stereotyped body rocking in a child. Rhythmic movement disorders usually begin in the first year of life and spontaneously remit by 4 years of age.
links.lww.com/CONT/A26

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Supplemental Digital Content 9-8

Rhythmic movement disorder. Video demonstrates head rocking movements in a 55-year-old woman with severe pulmonary sarcoidosis who was also diagnosed with obstructive sleep apnea and referred for a continuous positive airway pressure titration. During the study she was discovered to have these head rocking movements that arose out of N1 sleep. The results of her neurologic workup were normal. On subsequent history she mentioned that she has always rocked herself to sleep.
links.lww.com/CONT/A27

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