Restless Legs Syndrome
Case Study and Commentary, Allison Chan, DO, and Clete A. Kushida, MD, PhD

Restless legs syndrome (RLS) is a common neurologic condition affecting approximately 5% to 15% of the general population, although lower prevalence has been detected in some ethnic groups [1,2]. The mean age of onset is 27.2 years, but 38.3% of RLS patients develop the condition before age 20 [3]. Several studies indicate that prevalence increases with age [4,5]. Characterized by unpleasant sensations deep inside the legs, the disorder occurs at rest and is associated with an irresistible urge to move the legs. A majority of patients who have RLS are also found to have periodic limb movements during sleep, described as repetitive, stereotyped flexions of the hip, knee, and ankle. While about 70% to 90% of patients with RLS will demonstrate periodic limb movements on polysomnographic studies, one third of those with periodic limb movements will have RLS [6]. Pertinent details concerning RLS and periodic limb movement disorder (PLMD) and current treatment recommendations are presented in the following case study.

CASE STUDY
Initial Presentation
A 49-year-old woman presents to her primary care physician complaining about an uncomfortable feeling in both of her legs.

History
Present in a distribution distal to the knees, these dysesthesias began approximately 5 years ago and are appreciably worse in the late evening, particularly upon first getting into bed. She describes an irresistible urge to move her legs and finds that walking always eases the discomfort. Upon returning to bed, the irritating sensation promptly resumes. This problem has been steadily increasing in frequency over the past 2 years.

Her past medical history is significant for lumbago, bruxism, and 2 cesarean sections. She has no medication allergies.
and takes 2 to 4 acetaminophen tablets per week for her back pain. She uses an over-the-counter mouth guard at night for her bruxism. Her review of systems is notable for mild daytime fatigue, but she endorses a normal Epworth Sleepiness Score of 5/24. She has no evidence of snoring, witnessed apneas, somniloquy, somnambulism, gasping, choking, non-refreshing sleep, cataplexy, sleep paralysis, automatic behaviors, hypnagogic/hypnopompic hallucinations, gastroesophageal reflux disease, hypertension, cardiovascular disease, depression, anxiety, orthostatic hypotension, nausea, vomiting, constipation, diarrhea, or rectal bleeding. She is perimenopausal. She drinks 1 cup of coffee in the morning and a caffeinated soda at lunch but has no history of tobacco or illicit drug use. She consumes 1 alcoholic beverage per month. Her family history is significant for the presence of similar complaints of leg paresthesias from both her mother and younger sister. Their discomfort manifested late into her pregnancies and currently afflicts them on an intermittent basis.

**Physical Examination**

Physical examination reveals a weight of 152 lb, height of 63 in, body mass index of 27 kg/m², and neck circumference of 14 in. Oropharyngeal examination is significant for the presence of mild wearing on her molars but no evidence of temporomandibular joint dysfunction. Her hard palate is within normal limits, there are no teeth marks on her oral mucosa, and there is no evidence of maxillary or mandibular deficiency; sleep-disordered breathing would be suspected if positive findings for these features were observed. There is no focal tenderness over her spine or paraspinous muscles. The remainder of her examination is normal. Laboratory testing results are significant for a decreased ferritin level at 5 ng/mL and an increased transferrin level of 400 mg/dL.

**Table 1. IRLSSG Diagnostic Criteria for Restless Legs Syndrome**

| 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations. Sometimes the arms or other body parts are involved in addition to the legs. |
| 2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying down or sitting |
| 3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues |
| 4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present. |

IRLSSG = International Restless Legs Syndrome Study Group. (Adapted from reference 7. Copyright 2003, with permission from Elsevier.)

**How is RLS defined?**

In 2003, the International Restless Legs Syndrome Study Group (IRLSSG) convened to formulate new diagnostic criteria for RLS (Table 1) [7]. Patients may have difficulty describing their sensory symptoms, which are usually unpleasant but not painful. Descriptions include “creeping, crawling, tingling, cramping, pulling, pain, electric, tension, itching, stinging, nervousness, growing pains, and burning.” Symptoms are typically described as affecting the depth of the extremity rather than the surface of the skin. The majority of patients describe these symptoms occurring predominantly between the ankle and the knee, although the entire leg as well as the arms may be involved [8].

**How is RLS classified?**

RLS may be classified as either idiopathic (primary) or secondary [9]. Most patients with RLS suffer from the idiopathic form [10]. The secondary form may be seen with a variety of conditions, including iron deficiency, uremia, polyneuropathy, pregnancy, fibromyalgia, rheumatoid arthritis, Sjögren’s syndrome, radiculopathy, cobalamin deficiency, folate deficiency, and attention-deficit/hyperactivity disorder [11–20].

**What factors may be contributing to this patient’s RLS?**

Several factors are of particular interest in this patient. First, there is evidence of a family history of this disorder, suggesting an autosomal dominant mode of inheritance [21,22]. Her mother and sister both noticed an increase in their RLS symptoms during pregnancy. RLS may occur or worsen during pregnancy but typically resolves within a month after delivery. The history of back pain is of interest, although the patient has no evidence of either a radiculopathy or spinal stenosis. Additionally, the patient has evidence of iron deficiency anemia, and treatment for this condition should be considered.

Her history of bruxism and mild daytime fatigue raise suspicion for underlying sleep-disordered breathing. However, no findings on the physical examination of her airway provided anatomical evidence consistent with those typically seen in patients with obstructive sleep apnea.
RESTLESS LEGS SYNDROME

• What questions can help identify and characterize RLS?

The paresthesias and dysesthesias may be bilateral or unilateral. Volitional movements, like walking, stretching, or shaking the legs, attenuate the sensory symptoms for most patients. The severity of RLS symptoms can be assessed with the 10-question IRLSSG rating scale (Table 2). The patient must rate the symptoms on a scale of 0 to 4, with 0 representing none and 4 representing very severe [23]. PLMD is a condition characterized by limb movements during sleep that may lead to a complaint of insomnia or excessive daytime somnolence. Up to 80% of those with RLS also experience PLMD [3]. Periodic limb movements affect the lower extremities and are described as intermittent extension of the big toe and dorsiflexion of the ankle with occasional flexion of the knee and hip [24]. The movements are often bilateral but may predominate in 1 leg or alternate between legs [25]; they may affect the upper extremities and manifest as intermittent flexion at the elbow. Although periodic limb movements most frequently occur during the first half of the night, with a typical pattern of progressive decline through the rest of the night (as the amount of slow wave activity exponentially declines), they may also occur during wakefulness [26].

• What is the pathophysiology of RLS?

The pathophysiology of RLS and PLMD is unknown. Dopaminergic dysfunction is suspected given that RLS is highly responsive to dopaminergic agonists. RLS symptoms are characteristically worse with immobility and in the evening, a time when circadian levels of dopamine are lowest [27–29]. Research suggests that melatonin may contribute to exacerbation of RLS symptoms in the evening and through the night due to inhibitory effect on central dopamine secretion [30]. Based on positron emission tomography and single photon emission computed tomography (SPECT) findings, it has been postulated that RLS may be related to a mild nigrostriatal presynaptic dopaminergic hypofunction and decreased D2 receptor binding [31,32]. With the use of computerized movement analysis and SPECT, recent studies did not detect changes in central dopaminergic function [33,34].

RLS patients have been found to have low iron levels in their central nervous system, according to cerebrospinal fluid studies that demonstrate decreased levels of ferritin and increased levels of transferrin [35]. Magnetic resonance imaging studies have demonstrated decreased iron concentrations in the substantia nigra, and, to a lesser degree, the putamen, in patients with RLS [36]. Substantially reduced amounts of staining of both iron and H-ferritin in the substantia nigra have been identified in neuropathologic specimens of RLS patients [37]. One further important finding is that the sensory leg discomfort in RLS appears to be associated with cerebellar and thalamic activation per high-resolution functional MRI [38].

• What is the differential diagnosis for RLS?

One consideration in the differential is akathisia, which is an inner sense of restlessness and an urge to move; this disorder may appear in patients who use neuroleptics. Because subclinical respiratory effort–related arousals and subclinical hypopneas may result in periodic limb movements, it is important to evaluate for the presence of sleep-disordered breathing, such as obstructive sleep apnea or upper airway resistance syndrome; use of nasal continuous positive airway pressure may eliminate the periodic limb movements [39,40]. Often presenting with motor activity, an anxiety disorder must be a part of the differential diagnosis in RLS; however, this condition also presents with palpitations, sweating, and other signs of sympathetic involvement. Patients with “Vesper’s curse” may be aroused from sleep due to lumbar-sacral discomfort and leg paresthesias. These symptoms result from a transient lumbar stenosis that is due to venous plexus engorgement from increased right atrial filling pressure while

Table 2. IRLSSG Rating Scale

<table>
<thead>
<tr>
<th>Question</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overall, how would you rate the restless legs syndrome (RLS) discomfort in your legs or arms?</td>
<td>0–4</td>
</tr>
<tr>
<td>2. Overall, how would you rate the need to move around because of your RLS symptoms?</td>
<td>0–4</td>
</tr>
<tr>
<td>3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?</td>
<td>0–4</td>
</tr>
<tr>
<td>4. Overall, how severe is your sleep disturbance from your RLS symptoms?</td>
<td>0–4</td>
</tr>
<tr>
<td>5. How severe is your tiredness or sleepiness from your RLS symptoms?</td>
<td>0–4</td>
</tr>
<tr>
<td>6. Overall, how severe is your RLS as a whole?</td>
<td>0–4</td>
</tr>
<tr>
<td>7. How often (no. of days/week) do you get RLS symptoms?</td>
<td>0–4</td>
</tr>
<tr>
<td>8. When you have RLS symptoms how severe (no. of hours) are they on an average day?</td>
<td>0–4</td>
</tr>
<tr>
<td>9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs?</td>
<td>0–4</td>
</tr>
<tr>
<td>10. How severe is your mood disturbance from your RLS symptoms?</td>
<td>0–4</td>
</tr>
</tbody>
</table>

IRLSSG = International Restless Legs Syndrome Study Group. (Adapted from reference 23. Copyright 2003, with permission from Elsevier.)
lying down [41]. In a condition known as nocturnal paroxysmal dystonia, abrupt awakenings from nonrapid eye movement sleep may be followed by stereotypic dystonic movements. Another consideration is nocturnal leg cramps, which are uncomfortable spasms in the foot or calf; these can occur more often in association with musculoskeletal disorders, pregnancy, vigorous exercise, imbalances of fluids or electrolytes, and diabetes. It appears that children who have been diagnosed with attention-deficit/hyperactivity disorder exhibit significant amounts of motor activity at night [42]; this pediatric population may have exacerbation of their hyperactivity and inattentiveness from RLS-related motor activity as well as sleep fragmentation secondary to PLMD [43].

What are management strategies for patients with RLS?

Clinicians should evaluate and treat RLS patients for any secondary causes. Specifically, serum levels of iron, folate, ferritin, transferrin, cobalamin, creatinine, and urea should be measured if suspected. The etiology of iron deficiency should be investigated. Physicians should not treat patients with iron before measuring transferrin saturation and ferritin levels or before exploring a patient with a possible history of hemochromatosis, iron overload, or elevated pretreatment transferrin saturation. When oral iron supplementation is recommended, serum iron parameters should be measured at least 1 to 2 times per year [44]. In cases where upper airway resistance syndrome is suspected, a polysomnogram with esophageal manometry is indicated. Peripheral neuropathy can be evaluated via nerve conduction studies, electromyography, and serology (including hemoglobin A\textsubscript{1c}, thyroid-stimulating hormone, antinuclear antibody, serum protein electrophoresis, liver function tests, and rheumatoid factor).

Nonpharmacologic measures, such as sleep hygiene [45] and avoidance of exacerbating factors, may be beneficial. Patients should be made aware of the importance of eating properly, maintaining fixed times for bed and wake, and obtaining adequate amounts of sleep [46]. RLS and PLMD may both be exacerbated by antidepressants, including fluoxetine, sertraline, paroxetine, mirtazapine, and mianserin [47–52]. Caffeine has been shown to increase nervous system arousal and heighten the toxic sensory experience of RLS [53]. Patients with RLS and/or PLMD should avoid consumption of alcohol [54]. RLS may be induced by such neuroleptics as olanzapine and risperidone [55,56]. Symptoms may also be exacerbated by other agents, including lithium, \(\beta\) blockers, zonisamide, phenytoin, and methsuximide [57–60]. Engaging in physical activity near one’s bedtime, stress, and shift work may also exacerbate RLS [5].

Patients should be informed that pharmacotherapy will not cure RLS but may help to control or reduce symptoms. Clinicians should consider the patient’s age, as well as the severity and frequency of symptoms before initiating the most appropriate medication at a low dose and slowly titrating up as needed.

Iron deficiency can induce or perpetuate RLS [61]. It appears that ferritin levels higher than 50 \(\mu\)g/L are associated with less symptoms in RLS patients [62]. Patients may experience the phenomena of augmentation and/or rebound with treatment of their RLS and/or PLMD, specifically in the form of dopaminergic agents. In the phenomenon of augmentation, RLS symptoms may begin earlier in the day and become more severe than symptoms reported before treatment was started. Other limbs may become involved. Treatment options include changing to a dopamine agonist with a longer half-life or controlled-release levodopa, adding a dose in the middle of the night, or using a combination of regular-release and controlled-release levodopa [63,64].

Rebound occurs when the drug effect wears off, typically in the morning. It may be treated by using a lower dopaminergic dose, switching to a different dopaminergic medication that has a longer half-life or to a different class of medication (opioid or anticonvulsant), or decreasing the dose of the provocative medication [63–65].

Nonergotamine dopamine agonists (pramipexole and ropinirole) have largely become the first-line treatment of RLS. Although augmentation and rebound occur with these medications as well as other dopaminergic agents, they have proven very effective for RLS and PLMD patients and are associated with few side effects (eg, nausea, dizziness, orthostasis, insomnia, sleepiness).

Pramipexole has been shown to reduce the frequency of PLMS and the sensory discomfort of RLS [66]. A single bedtime dose, within the optimal range of 0.25 to 0.75 mg, controls symptoms through the night and into the next day.

Ropinirole, which is currently the only medication approved by the U.S. Food and Drug Administration for the treatment of RLS, has been studied with several double-blind, placebo-controlled studies and open-label trials [67–75]. With an optimal dose range of 0.25 to 4 mg, ropinirole dramatically decreases the sensory discomfort of RLS, even after 12 months from the initial treatment [76].

Ergotamine dopamine agonists that have demonstrated efficacy in managing RLS symptoms include pergolide, carbidopa, and bromocriptine. When administered at a mean dose of 0.51 mg 2 hours before bedtime, pergolide decreased RLS symptoms and periodic limb movements and also increased the total sleep time [77]. For patients who had developed augmentation with levodopa therapy or simply have severe RLS, carbidopa has been demonstrated to be efficacious in a range from 1 to 4 mg (mean dose, 2.1 mg) [78].
Bromocriptine subjectively improves paresthesias, restlessness, sleep efficiency, and frequency of periodic limb movements; it is typically initiated at a bedtime dose of 1.25 mg and may be increased to a total dose of 7.5 mg. However, side effects such as cardiac valvular disease have resulted in limited use of ergotamine dopamine agonists.

An effective means of controlling symptoms associated with Parkinson’s disease is to administer levodopa with a dopa decarboxylase inhibitor, such as carbidopa or benserazide. Taken 1 to 2 hours before bedtime, 1 to 2 tablets of carbidopa-levodopa 25/100 mg can decrease periodic limb movements and symptoms of RLS. Approximately 25% of patients experience rebound worsening of periodic limb movements in the morning after taking a bedtime dose [82]. If this problem should occur, or if symptoms occur later in the night, a controlled-release formulation of carbidopa-levodopa 50/200 mg can be administered. To improve sleep quality and to diminish symptoms from RLS and PLMD, regular-release levodopa and sustained-release levodopa may be given together [83,84]. Chronic treatment with levodopa, particularly at doses greater than 200 mg, often results in augmentation of RLS symptoms and periodic limb movements. Increasing the dose of levodopa in such situations only exacerbates the problems. It has been estimated that 13% to 70% of patients require medication change; switching to dopamine-agonist therapy often proves helpful [82,85].

Benzodiazepines, such as clonazepam, triazolam, alprazolam, and temazepam, have been studied to determine if they have a therapeutic role in RLS. Although a small clinical trial found clonazepam to be ineffective for treating RLS [86], 2 small double-blind studies showed that the sensory discomfort of RLS and the number of periodic limb movements were decreased by clonazepam [87–89]. The bedtime dose of clonazepam ranges from 0.5 to 2 mg. Triazolam decreases daytime sleepiness and improves sleep continuity and duration in patients with PLMD at a dose of 0.25 to 0.5 mg; it did not change the frequency of periodic limb movements but did decrease the frequency of associated arousals [90]. It appears that alprazolam may control symptoms of RLS [91]. Though a bedtime dose of 30 mg of temazepam addressed the insomnia associated with PLMD, it did not reduce the number of nocturnal myoclonic events [92].

Adrenergic agonists have been studied as well. Clonidine was found to decrease the symptoms of RLS but not the number of periodic limb movements at a daily dose of 0.05 mg [93]. The role of various antiepileptic medications, including gabapentin and carbamazepine, has been studied in RLS patients. At a starting bedtime dose of 300 mg, a mean dose of 800 mg, and a dose range between 300 and 1200 mg, gabapentin has been found to decrease the number of periodic limb movements and improve sleep architecture as well as the sensory and motor symptoms of RLS [94,95]. Furthermore, a head-to-head trial demonstrated that gabapentin and ropinirole were similarly effective in treating RLS and PLMD [96]. Though carbamazepine has been effective in reducing the sensory symptoms of RLS [97,98], this antiepileptic drug does not affect either the pattern of nocturnal myoclonus or its relationship to arousals during sleep [99].

At an average dose of 15.9 mg, oxycodone improves leg sensations, motor restlessness, and daytime alertness; it also decreases the number of arousals during sleep and periodic limb movements [100]. Patients with RLS and PLMD who were treated with opioids have long-term effectiveness ranging from 1 to 23 years [101]. When these patients are parenterally given naloxone, their signs and symptoms of RLS and PLMD return [102].

Treatment of RLS has been explored with other medications, including N-methyl-D-aspartate (NMDA) antagonists (eg, amantadine), folate, entacapone, bupropion, selegiline, and tramadol. Fifty-two percent of RLS patients improved at a daily dose of 100 mg of amantadine, which has a maximum daily dose of 300 mg and an average daily dose of 227 mg [103]. Patients with acquired folate deficiency or who have familial symptomatology may benefit from folate [104]. For patients experiencing end-of-dose wearing off, the catechol-O-methyl transferase inhibitor entacapone can be administered with each dose of levodopa/dopa decarboxylase inhibitor. The resulting enhancement of levodopa bioavailability is associated with reduced motor fluctuations [105–109]. Bupropion is not associated with antidepressant-induced PLMD; instead, it decreases the objective measures of PLMD [110]. Selegiline decreases the number of periodic limb movements [111]. A centrally acting analgesic with fewer side effects and lower abuse potential than opioids, tramadol was found to improve symptoms in a small number of RLS patients at a daily dose between 50 to 150 mg for 15 to 24 months [112]. Patients using a single dose of tramadol in the evening reported no major tolerance to the treatment effect.

**Treatment in this Patient**

Iron sulfate was begun at a dose of 325 mg once per day along with vitamin C 100 mg per day. Two months later, subsequent blood levels of ferritin and transferrin demonstrated values within normal ranges, but the patient noted no alleviation of her leg sensations or daytime fatigue. Her physician then prescribed clonazepam 0.5 mg at bedtime. After 6 weeks, the patient reported no improvement in any of her symptoms and asked to be discontinued from the benzodiazepine.

The patient was advised to monitor herself for any symptoms associated with sleep-disordered breathing (ie, snoring, witnessed breathing pauses, daytime sleepiness) as she continues to progress through menopause. She was continued...
on iron replacement therapy; follow-up levels of ferritin and transferrin 1 year later demonstrated normal values. Ropinirole was initiated at a bedtime dose of 0.25 mg. Although this dose helped alleviate most of her dysesthesias, further benefit was derived when the ropinirole was increased to 0.5 mg.

SUMMARY

Both RLS and PLMD are common disorders that can be detrimental to patients who experience frequent symptoms; these disorders can further lead to sleep fragmentation or insomnia and, therefore, daytime somnolence. Great strides have already been made in understanding the pathophysiology of these disorders and finding effective treatment options. As clinicians continue to complete thorough evaluations of patients like the case patient, they can rule out other underlying disorders and appropriately manage these populations of RLS and PLMD sufferers.

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References


CME EVALUATION: Restless Legs Syndrome

Directions: Each of the questions below is followed by 4 or 5 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following is NOT a secondary cause of restless legs syndrome (RLS)?
   (A) Fibromyalgia
   (B) Depression
   (C) Attention-deficit/hyperactivity disorder
   (D) Folate deficiency

2. Periodic limb movements do NOT
   (A) Predominate during the second half of the night
   (B) Affect the upper extremities
   (C) Alternate between legs
   (D) Occur during wakefulness
   (E) Affect 70% to 90% of patients with RLS

3. Which of the following statements is TRUE?
   (A) High-resolution functional MRI has demonstrated an association between cortical activation and leg discomfort in RLS patients
   (B) Increased levels of ferritin and transferrin have been reported in the cerebrospinal fluid of patients with RLS
   (C) RLS does not present in patients aged younger than 20 years
   (D) Circadian levels of dopamine are lowest in the evening
   (E) Neuropathologic specimens of RLS patients are likely to show an increase in iron staining in the substantia nigra

4. Which of the following statements about RLS management is FALSE?
   (A) Polysomnography with esophageal manometry may be warranted if upper airway resistance is suspected
   (B) Serology for liver function tests, rheumatoid factor, and antinuclear antibody should be done if peripheral neuropathy is suspected
   (C) High ferritin levels are indicative of secondary RLS
   (D) Sleep hygiene practices and avoiding alcohol and caffeine may be beneficial

5. Treatment options for RLS include
   (A) Neuroleptics, including risperidone and olanzapine
   (B) Ropinirole or pramipexole
   (C) Fluoxetine or sertraline
   (D) Maintaining a ferritin level below 50 µg/L
   (E) Exercising for 30 minutes before bedtime
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2. A  B  C  D  E
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4. A  B  C  D
5. A  B  C  D  E

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2. This article was fair, balanced, free of commercial bias, and fully supported by scientific evidence.
   __ Yes    __ No

3. Please rate the clarity of the material presented in the article.
   __ Very clear    __ Somewhat clear    __ Not at all clear

4. How helpful to your clinical practice was this article?
   __ Very helpful    __ Somewhat helpful    __ Not at all helpful

5. What changes will you make in your practice as a result of reading this article?
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