

Stilling the Nighttime Intruder: Innovations in Treatment of Restless Legs Syndrome (RLS)

Part 1 of 4: Overview of Restless Legs Syndrome

Dear Colleague:

According to the Restless Legs Foundation, “despite its offbeat name, RLS is a debilitating neurologic disorder that can lead to depression and even suicide” that afflicts almost 8% of the US population. Yet, only a small proportion of affected individuals seek medical care for their problem and even fewer are correctly diagnosed. People with RLS are typically sleep deprived, with profound negative effects on quality of life. Ironically, with medication RLS symptoms can be controlled for the great majority of affected individuals.

This is the first of a series of four *Treatment Reporters* on RLS. This issue presents an overview of RLS, including diagnostic criteria, epidemiology, differential diagnosis, and burden of illness. Upcoming issues will focus on specific suggestions regarding the key clinical steps for evaluating the patient suspected of having RLS in the primary care setting. Hypotheses regarding RLS pathophysiology will be discussed and factors that may precipitate RLS will be reviewed. We will then present practical treatment strategies for patients with RLS, including special populations, such as children, pregnant women, and the elderly.

We hope you find this series helpful and informative, and that the information presented can be incorporated into your clinical practice.

Yours truly,

Chair

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Overview of RLS

Restless legs syndrome (RLS) is a troublesome neurologic disorder that is often underrecognized and mistreated. First described in 1672 and given its name in 1945, RLS has been defined as having four core features, all of which are necessary for diagnosis.^{1,2}

- 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 and sometimes the arms or other body parts are involved in addition to the legs.)
- These urges to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying down or sitting.
- These urges 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.
- These urges 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.)

Although approximately 15% of affected individuals do not experience any sensation, the majority of patients report sensations in their legs ranging from creepy, crawling, bubbling, to burning, tingling, or pain, resulting in a desire to move. Symptoms usually affect both legs simultaneously, but can be unilateral or alternating, and the arms are also involved in almost half of patients.^{3,4} While symptoms may be worse at night, the key factors appear to be time of day and being supine, rather than sleep or darkness. About one fourth of patients with RLS experience symptoms on a daily basis.⁵

RLS is frequently associated with two common secondary features: poor sleep and periodic limb movements of sleep (PLMS), which are repetitive, stereotypic, involuntary movements, primarily of the legs, that occur during sleep. Poor sleep is reported in almost 95% of RLS patients who experience difficulties in sleep initiation, maintenance, and efficiency. Eighty percent of RLS patients have PLMS (index >5 movements/h sleep).⁴

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Watch Your Mail for the Next Issue of *Stilling the Nighttime Intruder: Innovations in Treatment of Restless Legs Syndrome (RLS)*

Download this 4-part series, *Stilling the Nighttime Intruder: Innovations in Treatment of Restless Legs Syndrome (RLS)*, available at www.projectsinknowledge.com/RLS/



Target Audience

This activity is designed for neurologists, pulmonologists, sleep specialists, psychiatrists, and primary care providers who treat patients with restless legs syndrome.

Activity Goal

The goal of this 4-part activity is to educate clinicians on the epidemiology, diagnostic criteria, appropriate evaluation, and effective management of primary and secondary restless legs syndrome.

Learning Objectives

After completing this 4-part activity, the physician should be able to:

- Discuss the epidemiology of RLS and the burden of illness it imposes on patients and society.
- Identify the diagnostic criteria for restless legs syndrome, differentiate between primary and secondary RLS, and assess the presence of coexisting sleep disorders.
- Compare the effectiveness, risks, and benefits of various pharmacologic and nonpharmacologic RLS therapies.
- Summarize the differences in mechanisms of action of RLS therapies.
- Develop practical strategies for treating patients with RLS using pharmacologic and nonpharmacologic therapies.
- Tailor treatment strategies to special patient populations, including the elderly with co-morbid disease, pregnant women, and children.

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Similar involuntary movements can occur in RLS patients during wakefulness when the patient is lying down or sitting. PLMS, which frequently occur with arousals and contribute to sleep disturbance, usually affect the legs and either resemble the Babinski reflex or a triple flexion reflex affecting the ankle, knee, and hip.³

Initially, symptoms may appear only occasionally but tend to become continuous and more severe with time. RLS can begin at any age, but most patients are middle to older age. In one study of 133 cases, the mean age for onset of RLS was 27.2 years and 43% of patients reported that their RLS symptoms began before age 20.⁴ Interestingly, patients whose RLS symptoms begin during middle age or later tend to deteriorate more rapidly and seek medical attention sooner than those whose symptoms begin during childhood.

RLS can be either primary or secondary. Primary RLS accounts for most cases and is believed to be of central nervous system origin. Secondary causes of RLS, some of which are potentially reversible, include iron-deficiency anemia, pregnancy, end-stage renal disease, and medications. These causes will be discussed in greater detail in a later section of this *Treatment Reporter*.

Burden of Illness

RLS is a major cause of sleep disturbance. Patients with RLS suffer from insomnia and disrupted sleep, leading to daytime fatigue, poor functioning at home or on the job, and impaired social interactions. Their restlessness causes them to walk around for hours at night and they may find it difficult to remain sedentary in school, while traveling, or while attending the theater or movies. Patients often feel embarrassed or ashamed, and depression and anxiety secondary to sleep deprivation may arise.

Epidemiology

The prevalence of RLS in the adult population has been estimated as ranging from 5.5% to 15%.⁶⁻⁸ Based on these estimates, between 11 million and 31 million American adults are affected by RLS symptoms. Of those, perhaps 1 out of 10 are affected seriously enough to need medical attention. RLS occurs about twice as frequently in women than men.⁹ The prevalence of RLS also increases with age. In a study of 1800 people in Kentucky, RLS prevalence increased from 3% in the 18- to 29-year-old group, to 10% in the 30- to 79-year-old group, to 19% in those age 80 years and older.⁷ RLS can occur in childhood and can be misdiagnosed as "growing pains" or attention-deficit-hyperactivity disorder (ADHD).^{10,11} The prevalence of RLS in children and adolescents is currently unknown.

Diagnosis and Work-Up of RLS

RLS is underreported by patients and often misdiagnosed. For example, in a large

multinational study of more than 23,000 people, less than half of the 2223 patients with RLS symptoms discussed the problem with their doctor and only 7.1% were actually diagnosed with RLS.⁵

The diagnosis of RLS can be made on history alone, probing the four obligatory diagnostic features of RLS. A neurologic examination should be done to rule out secondary causes of RLS, such as peripheral neuropathy or radiculopathy. A serum ferritin level should be drawn. If the serum ferritin level is in the bottom 1/3 of normal (<50 µg/L), then iron supplementation should be considered.^{2,3}

Generally, referral to a sleep specialist is not necessary to make the diagnosis of RLS, although polysomnography (PSG) and the Suggested Immobilization Test (SIT) can be used to support the clinical diagnosis. Polysomnography may reveal PLMS, but PLMS are neither a sensitive nor specific enough indicator of RLS to be useful diagnostically. Only 80% of RLS patients have PLMS and PLMS are found in a high percentage of elderly individuals without RLS. PSG is warranted if there is clinical suspicion of sleep apnea or patients do not respond to RLS treatment. In the SIT, the patient sits in bed with his or her legs outstretched during wakefulness while electromyograms (EMG) are recorded from right and left anterior tibialis muscles for an hour. The patient is asked not to voluntarily move. The SIT records periodic limb movements in wakefulness.¹²

Two rating scales have been developed for subjective rating of RLS symptom severity. One is a 10-point scale created by the International RLS Study Group that has been validated by comparison with independent clinician ratings in a large multicenter study.¹³ The other, the Johns Hopkins Restless Legs Severity Scale, is a one-question test that focuses on the time of day symptoms appear.¹⁴ Practically speaking, these assessment tools are used in research studies, but clinicians may find them useful for keeping track of therapeutic progress.

Differential Diagnosis

The most important differential diagnosis to consider is peripheral lesions, such as polyneuropathy and radiculopathy. Although peripheral neuropathy and radiculopathy may trigger RLS, the bulk of these patients do not have RLS. Although patients with peripheral neuropathy and radiculopathy may complain about paresthesias or painful sensations, those without RLS typically do not get relief of leg discomfort with activity. Nerve conduction or EMG studies may be informative for these patients.

Sometimes RLS may be mistakenly misdiagnosed as leg cramps. Leg cramps are usually brief, intermittent, and severe with a localized spasm, while RLS tends

to last longer with no actual spasm. Neuroleptic-induced akathisia is also characterized by restless floor pacing. However, in neuroleptic-induced akathisia, movement is precipitated by an inner urge to move rather than the leg discomfort of RLS and, unlike RLS, there is no nighttime worsening of symptoms. Neuroleptic-induced akathisia can be suspected if the patient has a history of neuroleptic use. Patients with positional pain, eg, due to arthritis of one hip, will get relief merely by shifting the weight from one hip to another while sitting and they are not compelled to walk, stretch the legs, or bend the legs as in RLS. Hypotensive akathisia and the syndrome known as Painful Legs and Moving Toes are rare conditions that can be distinguished from RLS. A comparison of these differential diagnoses and their distinguishing features from RLS are listed in *Table 1*.

lumbosacral generator to fire, thus producing PLMS.¹⁷

A body of evidence suggests that RLS involves a disruption of subcortical dopamine systems.¹⁶ Support for this hypothesis stems from the observation that RLS symptoms respond to dopaminergic agonist treatment and are exacerbated by centrally acting dopaminergic antagonists.^{16,18-20} Small decreases in striatal dopaminergic measures have been found in four positron emission tomographic (PET) and single photon emission computed tomographic (SPECT) studies of RLS patients (see Allen and Earley¹⁶ for a review). The observed deficits are both pre- and post-synaptic.

A current hypothesis undergoing exploration is that RLS results from a deficiency of dopaminergic function based on abnormalities of iron transport and

exacerbates the symptoms of RLS. This indicates that the opiate effect is specific to the opioid receptor and implicates the endogenous opiate system in the pathogenesis of RLS.²⁷

Associated Conditions

Table 2^{28,29} lists the more well-established other medical conditions associated with and, in some cases, possibly causal to the symptoms of RLS. RLS has been noted in about 20% of women who are pregnant^{22,30} and in 20% to 62% of patients with kidney failure undergoing dialysis.^{31,32} Medications that can precipitate RLS include tricyclic and selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, lithium, antihistamines, and typical and atypical neuroleptics.^{3,6,33}

Table 2. Conditions Associated with RLS^{28,29}

- Iron-deficiency anemia
- Pregnancy
- End-stage renal disease
- Medications (neuroleptics/antidepressants)
- Rheumatoid arthritis
- Polyneuropathy/radiculopathy

Table 1. Differential Diagnosis of RLS

	Paresthesias/ Dysesthesia	Movement	Symptoms at Rest Relieved with Activity	Worsening of Symptoms at Night	Comments
RLS	✓	Walking, stretching bending legs to relieve paresthesias and dysesthesias	✓	✓	
Peripheral neuropathy	✓		No relief with activity		
Leg cramps	✓	Pushing foot against bed or floor to relieve cramp	✓	Sometimes nocturnal	Brief, intermittent, severe, localized pain, spasm
Neuroleptic- induced akathisia		Walking, marching-in- place, body rocking		No nighttime worsening	Neuroleptic use
Painful legs/ moving toes	✓	Involuntary movements of toes			
Positional pain	✓	Patient shifts weight while sitting	✓		Relieved by shifting position

What Causes RLS?

Pathophysiology

The origin and pathophysiology of RLS are still under investigation. RLS is thought to result from a complex interaction between central and peripheral neurologic systems. Bara-Jimenez et al¹⁵ observed that patients with RLS had evidence of enhanced spinal cord excitability compared with age-matched controls, especially at night. Studies of cortical activity have failed to find evidence of a primary cortical involvement in RLS, and other studies suggest a subcortical dysfunction.¹⁶ Functional MRI studies, paired transcranial magnetic stimulation studies, examination of the cortical silent period, examination of the flexor response, examination of the sequential activation of muscle groups, and evidence from spinal cord injury cases are most consistent with the hypothesis that, under normal conditions, a subcortical brain stem generator inhibits a lumbosacral generator for PLMS. The abnormal legs sensations from RLS may overcome the brain-stem inhibition and cause the

storage.²¹ Several lines of evidence support this. Iron is linked to dopamine as it is a necessary co-factor for tyrosine hydroxylase, the rate-limiting enzyme in the conversion of levodopa to dopamine. Iron deficiency anemia is one of the secondary causes of RLS,¹⁶ and is common in several other secondary causes, including end-stage renal disease and pregnancy.^{22,23} Furthermore, correction of the peripheral iron problem often reduces or resolves RLS symptoms.²⁴ Even in the absence of anemia, the severity of RLS increases with serum ferritin concentrations lower than 50 µg/L.²⁵ MRI studies show that brain iron values appear to be particularly important, with decreased iron stores in the substantia nigra.²⁶ Recently, the onset of RLS was correlated with iron deficiency due to multiple blood donations.²⁴

Another hypothesis is that there is a hypofunction of the endogenous opioid system in RLS. Opioids improve RLS symptoms and administration of the rapidly acting opioid receptor blocker naloxone to opioid-treated patients

The relationship of RLS to exercise is complex. Although walking relieves RLS symptoms while the patient is actually walking, excessive exercise earlier in the day can exacerbate symptoms later that night. On the other hand, regular exercise and maintaining a good lifestyle are associated with less severe symptoms of RLS. Hypertension, heart disease, sleep apnea and arthritis are also more common in RLS, although the reasons for these associations are unclear. While the prevalence of RLS is increased in patients with rheumatoid arthritis, the reverse is not true, ie, the prevalence of rheumatoid arthritis is not increased in patients with RLS. It is still controversial as to whether or not there is a link between RLS and Parkinson's disease, a known dopaminergic deficiency disorder.^{6,7,33-35}

Risk Factors

Several risk factors have been identified for RLS. The first is age, with increasing age associated with increasing prevalence and severity.⁷ There also appears to be a genetic predisposition to developing RLS. RLS is often familial and most studies show an autosomal dominant form of inheritance. Reports have shown that up to 92% of family members of people with idiopathic RLS show RLS symptoms.^{4,36}

Overview of Treatment Strategies

Generally nonpharmacologic therapies for RLS result in poor and temporary responses. Educating the patients about steps to improve sleep hygiene can be beneficial because poor sleep habits and sleep disruption can aggravate RLS. Some patients

find that hot baths, muscle stretching in the morning and night, delayed sleep and rise times, massage, or moderate exercise are helpful.³³ Leg vibration, nonelectric or electric stimulation, acupuncture, or sleeping on a hard floor have been tried, but most patients seeking treatment require medications.^{23,37}

Symptoms of RLS do respond well to pharmacologic therapy. Currently about one third of patients can achieve “great relief,” one third “significant relief,” and one third “some relief.” Only about 5% of patients are totally refractory to current therapies. Several pharmacologic approaches to treating RLS relate to specific deficits that contribute to RLS. For instance, iron replacement and perhaps vitamin B12 and folate supplementation can help patients with RLS. A serum ferritin in the bottom 1/3 of normal (<50 µg/L) is an indication for treatment. Earley²³ recommends 65 mg of elemental iron along with 100 mg of vitamin C on an empty stomach one to three times daily and determination of the ferritin level and iron saturation after 3 months. Oral iron supplementation should be contin-

ued until ferritin levels are at or above 50 µg/L and iron saturation is >20%.

Women should be informed that RLS symptoms often diminish or disappear after pregnancy. It is better to be conservative in the treatment of RLS in pregnancy, particularly in the first trimester, although iron, vitamin B12 and folate can generally be used safely. In some cases, however, the symptoms of RLS in pregnancy are severe enough to warrant further treatment.

In general, dopamine agonists and levodopa are now the first-line treatments for idiopathic or familial RLS.³⁸ These agents include two ergot-derived agents, bromocriptine and pergolide, and two nonergot medications, pramipexole and ropinirole. Dopaminergic agents provide symptom relief to 90% of RLS patients and reduce the frequency of PLMS by 70% to 100%.²³

Second-line options for the treatment of RLS include opiates (propoxyphene, codeine, oxycodone, methadone), benzodiazepine sedative hypnotic agents (clonazepam, diazepam) and

anticonvulsants (gabapentin). The anticonvulsants are particularly appropriate for painful RLS symptoms.

Summary

RLS is a common, debilitating neurologic disorder that is poorly recognized by patients and physicians alike. With this in mind, it is incumbent upon clinicians to query patients about the quantity and quality of sleep, nighttime awakenings, and daytime sleepiness. A bed partner can be a key source of information about the patient's habits that may not be evident to the patient.

The clinician should also inquire about risk and other dietary, metabolic, and lifestyle factors that may precipitate RLS symptoms. Once RLS is diagnosed, the clinician can utilize pharmacologic treatment strategies that focus on correcting iron deficiency or stimulating dopaminergic pathways to provide significant symptom relief.

The next *Treatment Reporter* will review the evidence supporting specific treatment paradigms for RLS. TX

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CME Posttest

Part 1 of 4: Overview of Restless Legs Syndrome

Stilling the Nighttime Intruder: Innovations in Treatment of Restless Legs Syndrome (RLS)

CME Instructions

To receive documentation of your participation in this 4-part CME activity (for which each newsletter equals .25 hour for a total of 1 hour of CME credit), please complete the following steps:

1. Read each *Tx Reporter* newsletter carefully.
2. Complete the CME Posttest included in each of the newsletters, selecting the most appropriate response to each question.
3. Complete the CME Evaluation Survey which will be included at the end of Newsletter #4.
4. Mail or fax each of your completed CME Posttests and the final CME Evaluation Survey to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 1-973-890-8866.*

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Please select the most appropriate response to each question.

1. A 50-year-old was diagnosed with painful peripheral neuropathy. She does not feel the need to move to relieve her leg discomfort and movement does not give her relief. Does she have RLS?
 Yes No
2. A 70-year-old man presents with complaints of numbness, tingling, and nighttime pain in his legs. He denies any relief from walking or bending the legs, but does find shifting his weight using a pillow under his hip to be helpful. Does he have RLS?
 Yes No
3. Which of the following is necessary to make the diagnosis of RLS?
 Polysomnography
 Serum ferritin level
 Sensory/motor physical exam
 None of the above
4. Which of the following are not considered a secondary cause of RLS?
 Pregnancy
 End-stage kidney disease
 Hypoxia
 Medications
5. What are some strategies to consider when treating RLS?
 Resolve iron deficiency
 Use a benzodiazepine, hypnotic or opioid
 Treat with a dopaminergic agonist or L-DOPA.
 Treat with an anticonvulsant like gabapentin
 All of the above