

RESTLESS LEGS SYNDROME

DETECTION AND MANAGEMENT IN PRIMARY CARE

INTRODUCTION

Restless legs syndrome (RLS) is a common, underdiagnosed, and treatable condition. A neurologic movement disorder, RLS is often associated with a sleep complaint.¹ Patients with RLS can suffer an almost irresistible urge to move the legs, usually due to disagreeable leg sensations that are worse during inactivity and often interfere with sleep.² RLS can be described as an agitated inability to rest that can have a negative impact on the quality of life due to waking discomfort, chronic sleep deprivation, and stress. This publication provides science-based information about RLS and its assessment and management in the primary care setting.

CONSEQUENCES OF RLS

Direct results of RLS include discomfort, sleep disturbances, and fatigue.³ These consequences have a secondary impact on functioning by affecting occupational activities, social activities, and family life. Disrupted sleep and an inability to tolerate sedentary activities can lead to job loss, a compromised ability to enjoy life, and problems with relationships.

PREVALENCE

RLS is a common disorder. Although the exact prevalence is uncertain, limited studies have indicated that 2 to 15 percent of the population may experience RLS symptoms.^{4,5,6} This wide range may be due to differences in study methodologies.

Although the prevalence of RLS increases with age⁶, it has a variable age of onset and can occur in children.⁷ In patients with severe RLS, one-third

to two-fifths had their first symptom before age 20⁸, although the precise diagnosis of RLS was made much later.

ETIOLOGY

Primary RLS

RLS is a central nervous system (CNS) disorder.⁹ It is not caused by psychiatric factors or by stress but may contribute to or be exacerbated by these conditions. There is a high incidence of familial cases of RLS, suggesting a genetic origin for primary RLS.⁸ The exact mode of inheritance is unknown.^{8,10}

Secondary Causes of RLS

- **Iron deficiency.** RLS may be associated with iron deficiency. A patient's iron stores may be deficient without significant anemia. Recent studies have shown that decreased iron stores (indicated by ferritin levels below 50 mcg/L) can exacerbate RLS symptoms.^{11,12} Patients with newly diagnosed RLS or RLS patients with a recent exacerbation of symptoms should have their serum ferritin levels measured.
- **Neurologic lesions.** RLS has been reported in association with spinal cord and peripheral nerve lesions, although an exact pathological mechanism has not been identified. RLS may also emerge in patients with vertebral disc disease.⁸
- **Pregnancy.** RLS affects up to 19 percent of women during pregnancy.¹³ Symptoms can be severe but usually subside within a few weeks postpartum.

- **Uremia.** RLS occurs in up to 50 percent of patients with end-stage renal failure, and may be particularly bothersome during dialysis when the patient is confined to a resting position.^{14,15} Improvement in RLS symptoms has been seen after renal transplantation.¹⁶
- **Drug-induced.** There is some evidence from published case reports that RLS symptoms may be worsened or unmasked by medications such as tricyclic antidepressants,¹⁷ selective serotonin reuptake inhibitors (SSRIs),¹⁸ lithium,¹⁹ and dopamine antagonists.²⁰ Caffeine also has been implicated in the worsening of RLS symptoms.²¹

ASSESSMENT AND DIAGNOSIS

The diagnosis of RLS is based primarily on the patient’s history. Often, patients do not bring RLS symptoms to the physician’s attention; therefore, it can be helpful to include general sleep questions in the review of systems. See Appendix. When

RLS is suspected, more specific questions can be asked. See Table 1.

Symptoms are described by patients in many ways, ranging from mild to intolerable.²² See Table 2. Although most patients experience the sensations in their legs, the sensations may also occur in the arms or elsewhere. RLS symptoms are generally worse in the evening and night and less severe in the morning. RLS needs to be distinguished from sleep-related leg conditions such as nocturnal leg cramps.

Clinical Criteria

The following criteria for diagnosis of RLS are based on those developed by the International Restless Legs Syndrome Study Group.³

Minimal criteria include the following:

1. A compelling urge to move the limbs, usually associated with paresthesias/dysesthesias.

Table 1

RLS-RELATED QUESTIONS
■ Does the patient report “creeping, crawling, or uncomfortable, difficult-to-describe feelings” in the legs or arms that are relieved by moving or rubbing them?
■ Is there a correlation between RLS symptoms and time of day? Do the symptoms worsen with rest or inactivity?
■ Do sensations interfere with sleep onset or returning to sleep?
■ What daytime consequences does the patient report (e.g., fatigue, sleepiness, confusion, lack of attention)?
■ Does the bed partner report that the patient’s legs or arms jerk during sleep? (Relates to periodic limb movements in sleep.)
■ Does the patient have secondary causes of RLS such as low iron stores, diabetes mellitus, kidney disease, or pregnancy?
■ Are neurological symptoms or diagnoses present?
■ Is there a relationship between symptoms and medications, such as tricyclic antidepressants or SSRIs?
■ Was the onset of symptoms correlated with a change in medication?
■ Do family members report similar symptoms? Have family members been diagnosed with RLS?

Table 2

TERMS USED TO DESCRIBE RLS SENSATIONS		
Creeping	Indescribable	Electric current-like
Crawling	Pulling	Restless
Itching	Drawing	Painful
Burning	Aching	
Searing	Like water flowing	
Tugging	Like worms or bugs crawling under the skin	

2. Motor restlessness as seen in activities such as floor pacing, tossing and turning in bed, and rubbing the legs.
3. Symptoms worse or exclusively present at rest (i.e., lying, sitting) with variable and temporary relief by activity.
4. Symptoms worse in the evening and at night.

Other associated features commonly found in RLS but not required for diagnosis include the following:

- Sleep disturbance and daytime fatigue.
- Normal neurological exam in primary RLS.
- Involuntary, repetitive, periodic, jerking limb movements, either in sleep or while awake and at rest.

The last feature refers to periodic limb movements (PLM), also known as PLMS (periodic limb movements of sleep)²³ or nocturnal myoclonus,²⁴ which may be associated with RLS. PLM are stereotyped, repetitive flexions of the limbs (legs alone or legs more than arms) usually occurring during sleep. They occur periodically on an average of every 20 seconds. The most common movement is a dorsiflexion of the ankles and flexion of the knees or hips.

Physical Examination

The physical examination is usually normal in patients with RLS and is performed to identify secondary causes and rule out other disorders. The following are areas of particular importance:

- *A neurological exam* with emphasis on spinal cord and peripheral nerve function.
- *A vascular exam* to rule out vascular disorders.

Laboratory Tests

The following laboratory tests can identify possible secondary causes of RLS:

- Serum ferritin level (<50mcg/L)
- Serum chemistry to rule out uremia and diabetes

A sleep study (polysomography) is **not** routinely indicated in the workup of RLS²⁵ because RLS is diagnosed on the basis of history and clinical findings.

Differential Diagnosis

Differential diagnoses may include the following:

- Nocturnal leg cramps (typically painful, palpable, involuntary muscle contractions, often focal, with a sudden onset; usually unilateral).²⁶

Table 3

PHARMACOLOGIC TREATMENT FOR RLS		
Agent	Advantages	Disadvantages
Dopaminergic Agents Dopamine precursor combinations such as carbidopa-levodopa	Can be used on a “one time” basis or as circumstances may require. Useful for persons with intermittent RLS because dopamine agonists take longer to have an effect.	As many as 80 percent of patients on carbidopa-levodopa may develop augmentation.* Therapeutic effect may be reduced if taken with high-protein food. Can cause insomnia, sleepiness, and gastrointestinal problems.
Dopamine agonists such as Pergolide Pramipexole Ropinirole	Useful in moderate to severe RLS. Recent reports indicate high efficacy of dopamine agonists, but the role of their long-term use is unknown. ²⁹	Can cause severe sleepiness, ³⁰ which may limit its use during daytime. Agonists can cause nausea. To avoid this, slow dose increase is important, especially for pergolide.
Opioids such as Codeine Hydrocodone Oxycodone Propoxyphene Tramadol	Can be used on an intermittent basis. Can also be used successfully for daily therapy.	Can cause constipation, urinary retention, sleepiness, or cognitive changes. Tolerance and dependence possible with higher doses of stronger agents.
Benzodiazepines such as Clonazepam Temazepam	Helpful in some patients when other medications are not tolerated, and may help improve sleep.	Can cause daytime sleepiness and cognitive impairment, particularly in the elderly.
Anticonvulsants such as Carbamazepine Gabapentin	Can be considered when dopamine agonists have failed. May be useful in those with coexisting peripheral neuropathy and/or when RLS discomfort is described as pain.	Disadvantages vary depending on agent, but include gastrointestinal disturbance such as nausea, sedation, dizziness.
Iron (ferrous sulfate)	Use in patients with serum ferritin levels <50 mcg.	Ideal means of administration has not been established. Oral treatment may take several months to be effective and may be poorly tolerated.
Clonidine	May be useful in hypertensive patients.	Has the potential to cause hypotension, dermatitis, and sleepiness.

*Augmentation is a worsening of RLS symptoms in the course of therapy. Symptoms may be more severe and start earlier in the day (e.g. afternoon rather than evening) than before treatment began and may spread to different parts of the body. Augmentation, which can start soon after therapy is begun or not until months or years later, has also been reported with dopamine agonists and may occur with other medications.

- Akathisia (excessive movement, without specific sensory complaints; often does not correlate with rest or time of day and usually results from medication such as neuroleptics or other dopamine blocking agents).²⁷
- Peripheral neuropathy (can cause leg symptoms that are different from RLS; they are usually not associated with motor restlessness, nor helped by movement, and have no evening or night time worsening. Sensory complaints are typically numbness, tingling, or pain. Small fiber sensory neuropathies, as seen in diabetes, are often confused with RLS. Patients with neuropathies may have both neuropathic and RLS symptoms.)
- Vascular disease (such as deep vein thrombosis).

TREATMENT

The severity of RLS varies from patient to patient. Although pharmacologic treatment is helpful for many RLS patients, those with mild symptoms may not need medications. Since no single medication or combination of medications will work predictably for all patients, treatment must often be individualized. Physicians and patients may need to work together over time to find the medication or combination of medications and the dosages that will work best. See Table 3 for a list of pharmacologic agents and their advantages and disadvantages. Therapy for RLS constitutes an “off label” use of these pharmacologic agents.

The selection of pharmacologic agents is influenced by a number of factors, including:

- Age of the patient. (For example, benzodiazepines may cause cognitive impairment in the elderly.)
- Severity of symptoms. (Some patients with mild symptoms may elect not to use medications; others may benefit from levodopa or a dopamine agonist. Patients with severe symptoms may require a strong opioid.)
- Frequency or regularity of symptoms. (Patients with infrequent symptoms may benefit from a single effective p.r.n. dose of a medication such as an opioid or levodopa.)
- Presence of pregnancy or comorbid illnesses. (There are no controlled clinical trials that have assessed the safety and efficacy of medications for RLS or PLM during pregnancy.²⁸)
- Renal failure. (In these patients, pharmacologic agents are generally safe, but less frequent doses may be needed if drugs are renally excreted. In addition, for dialysis patients, some medications are dialyzable [e.g., gabapentin] and others are not [e.g., propoxyphene].²⁸)

Dopaminergic agents are the first-line drugs for most RLS patients. It is important for the primary care physician to educate the patient about the nature and actions of the drugs that are prescribed, including side effects and the uncertainty of long-term effects. For example, when prescribed dopaminergic agents, the patient should be informed that although these medications are usually used to treat Parkinson’s disease, they also help to relieve RLS symptoms.

RLS medications have received approval from the Food and Drug Administration for other uses. In many cases, the therapeutic doses to treat RLS are much lower than those required for the original uses. The starting dose is usually very low and is gradually increased until effective. In addition to the medications listed in Table 3, agents such as vitamin E, folate, and magnesium may be useful. Although many nonpharmacologic treatments have been reported by patients to be helpful, there is no scientific evidence that they are useful in the treatment of RLS.

WHEN TO CONSIDER REFERRAL

For most patients, RLS can be effectively managed by the primary care physician. If the primary care physician encounters difficulty managing RLS symptoms in a patient, referral to, or consultation with, a movement disorders specialist or a sleep specialist may be helpful.

CONCLUSION

The primary care physician plays a central role in the identification and treatment of RLS. Incorporating sleep- and RLS-related questions into the general review of systems can be helpful in diagnosing RLS. An important aspect of treatment is listening to and supporting patients and carefully evaluating their complaints. Most patients with RLS can obtain symptomatic relief with commonly prescribed medications and support.