Restless Legs Syndrome: A Comprehensive Review for Primary Care Physicians

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Abstract

Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a common chronic neurological sensorimotor disorder characterized by an overwhelming urge to move the legs, usually accompanied by unpleasant sensory symptoms. The disorder affects sleep quality, daytime functioning, mental health, and overall quality of life. RLS is frequently encountered in primary care yet remains significantly underdiagnosed and undertreated. Primary care physicians play an important role in the detection, evaluation, and management of RLS. This review provides an evidence-based overview of epidemiology, pathophysiology, diagnosis, differential diagnosis, and current management strategies relevant to primary care.

Keywords: Restless Legs Syndrome; Willis-Ekbom Disease; Primary Care; Iron Deficiency; Alpha-2-Delta Ligands; Dopamine Agonists; Augmentation

Introduction

Restless Legs Syndrome (RLS) is a neurological disorder characterized by an irresistible urge to move the limbs, predominantly the legs, associated with unpleasant sensations that worsen during periods of rest and improve with movement. Symptoms typically become more prominent during the evening and night-time hours (1).

RLS is fundamentally a sensorimotor neurological condition. The disorder may present as either primary (idiopathic) or secondary to various medical conditions including iron deficiency, pregnancy, chronic kidney disease (CKD) and peripheral neuropathy (2).

RLS can cause major sleep disruption. These patients also commonly experience fatigue, impaired concentration, mood disturbances, reduced productivity, and cardiovascular consequences related to chronic sleep deprivation (3,4). Recognition of RLS in primary care is therefore essential for improving patient outcomes and reducing disease burden.

Epidemiology

RLS is among the most common neurological disorders encountered in outpatient practice. Population studies estimate that the overall prevalence is 5–10% of adults (3,5).

RLS occurs in both sexes but is approximately twice as common in women. The prevalence increases progressively with age, although symptoms may begin during childhood or adolescence (5).

Risk Factors

Several factors are associated with increased risk (Table 1).

Table 1: Risk factors for RLS

Modifiable risk factors	Non-modifiable risk factors
Iron deficiency / low ferritin levels	Increasing age
Excessive caffeine intake	Female sex
Alcohol consumption	Family history of RLS
Smoking / tobacco use	Genetic predisposition
Sleep deprivation or poor sleep hygiene	Inherited (primary) RLS
Obesity	Pregnancy (especially third trimester)
Physical inactivity	Certain underlying neurological predispositions
Certain medications (e.g., antidepressants, antihistamines, antipsychotics, dopamine antagonists)	
Poorly controlled diabetes mellitus	
Peripheral neuropathy due to treatable causes	
CKD (especially if poorly managed)	
Vitamin and mineral deficiencies (iron, folate, etc.)	

Pathophysiology

The pathogenesis of RLS is multifactorial and incompletely understood. Current evidence implicates a combination of iron dysregulation, dopaminergic dysfunction, and genetic susceptibility (6).

Brain Iron Deficiency
Iron plays a crucial role in dopamine synthesis and dopamine receptor function. Studies demonstrate reduced iron concentrations within the substantia nigra and other brain regions involved in motor control (7). Importantly, patients may have normal serum haemoglobin levels while exhibiting reduced brain iron stores (8).

Dopaminergic Dysfunction
The effectiveness of dopamine agonists and alterations in dopamine metabolism support a central role for dopaminergic dysfunction. Abnormalities involve reduced dopamine receptor activity, altered circadian dopamine regulation, and dysfunctional nigrostriatal pathways. Symptoms typically worsen in the evening, coinciding with physiological reductions in dopaminergic activity.

Genetic Factors
Approximately 40–60% of patients with early-onset disease report a family history of RLS. Familial RLS usually presents earlier and tends to follow a more chronic course.

Clinical Features

Patients commonly describe:
- An irresistible urge to move the legs
- Restlessness
- Crawling sensations
- Tingling
- Pulling sensations
- Burning discomfort
- Itching deep within the legs
- Electric shock-like sensations

The sensations are difficult for patients to describe and are often referred to as occurring “inside the legs.” Symptoms demonstrate four characteristic features.

1 Occurrence during Rest
Symptoms appear or worsen during:
- Sitting
- Lying down
- Long-distance travel
- Sedentary activities

2 Relief with Movement
Patients experience temporary improvement through:
- Walking
- Stretching
- Leg movements
- Pacing
- Massaging affected limbs

3 Circadian Pattern
Symptoms are:
- Minimal during the morning
- Progressive throughout the day
- Maximal during the evening and night-time

4 Recurrent Nature
Symptoms occur repeatedly and may become chronic.

Diagnostic Criteria

The International Restless Legs Syndrome Study Group (IRLSSG) defines five essential diagnostic criteria (1) (Table 2).

Table 2: IRLSSG essential diagnostic criteria for RLS (1)

Criterion	Description
1	An urge to move the legs, usually accompanied by uncomfortable sensations
2	Symptoms begin or worsen during periods of rest or inactivity
3	Symptoms are partially or completely relieved by movement
3	Symptoms are worse in the evening or at night than during the day
5	Symptoms cannot be explained solely by another medical or behavioural condition

Clinical Evaluation in Primary Care

A detailed history remains the cornerstone of diagnosis (9).

Medication Review
Numerous medications can worsen RLS symptoms (10).

Common offenders include:
- **Antidepressants:** fluoxetine, sertraline, escitalopram, venlafaxine
- **Antihistamines:** diphenhydramine, chlorpheniramine
- **Dopamine antagonists:** metoclopramide, prochlorperazine
- **Antipsychotic medications:** risperidone, olanzapine, haloperidol

Physical Examination
Physical examination is usually normal in primary RLS. The primary purpose of examination is to identify secondary causes.

Investigations
Although RLS is a clinical diagnosis, laboratory testing helps identify secondary causes.

Iron studies:
- Serum ferritin
- Transferrin saturation
- Serum iron
- Total iron-binding capacity

Current guidelines recommend evaluation of iron status in all patients (11–13).

Additional laboratory tests:
• Complete blood count
• Renal function tests
• Liver function tests
• Thyroid-stimulating hormone
• Fasting blood glucose or HbA1c
• Vitamin B12
• Folate
• Magnesium (selected patients)

Causes of Secondary RLS

Iron Deficiency
The most common reversible cause (13).

Pregnancy
Occurs in approximately 10–30% of pregnancies (14,15).
Characteristics:
- Most common during the third trimester
- Associated with reduced iron stores
- Usually resolves postpartum

Chronic Kidney Disease
RLS affects up to one-third of dialysis patients (2).

Neurological Diseases
- Peripheral neuropathy
- Parkinson disease
- Multiple sclerosis
- Spinal cord disorders

Differential diagnosis

- Nocturnal leg cramps
- Akathisia
- Peripheral neuropathy
- Peripheral vascular disease
- Positional leg discomfort

Management

Treatment Goals
Management aims to:
- Reduce symptom severity
- Improve sleep quality
- Enhance daytime functioning
- Improve health-related quality of life
- Prevent treatment-related complications

Non-Pharmacological Management
Recommended for all patients. Lifestyle modification includes:
• **Sleep hygiene:** fixed bedtime routines, a regular sleep schedule, minimal screen time before bed, and a quiet sleep environment.
• **Exercise:** moderate regular exercise improves symptoms. Patients should avoid excessive strenuous exercise and late-night vigorous workouts.
• **Avoiding triggering substances**: reduction or avoidance of caffeine, nicotine, and alcohol.
• **Symptomatic relief measures:** walking, stretching, leg massage, warm baths, heating pads, and cold compresses.

Iron Therapy
Oral iron: Recommended when ferritin is below normal or in the low-normal range (11,13). Typical regimen:

- Ferrous sulfate providing 65 mg elemental iron
- Combined with vitamin C to enhance absorption

Intravenous iron: Considered when:
- Oral therapy fails
- Severe symptoms exist
- Iron absorption is impaired
- Rapid symptom improvement is desired

Intravenous iron has demonstrated significant benefit in appropriately selected patients (13,16).

Pharmacological Therapy
Recent treatment guidelines increasingly favour alpha-2-delta calcium channel ligands as first-line agents (11,12,17,18) (Table 3).

Table 3: Pharmacological treatment options for RLS

Drug class	Medications
Alpha-2-delta ligands (first-line)	Gabapentin, gabapentin enacarbil, pregabalin
Dopamine agonists	Pramipexole, ropinirole, rotigotine patch
Opioids (refractory RLS)	Oxycodone/naloxone, methadone, buprenorphine, tramadol
Benzodiazepines (adjunctive)	Clonazepam, temazepam

Augmentation
Augmentation is the most important long-term complication of dopaminergic therapy (12,19). Symptoms:
- Appear earlier in the day
- Become more severe
- Spread to the arms or trunk
- Respond less effectively to treatment

Recognition is critical because increasing the dopamine agonist dose often worsens the condition.

Refractory RLS
Refractory disease is defined as persistent symptoms despite adequate treatment. Management strategies include:

- Reassessing iron stores
- Correcting aggravating factors
- Switching medication classes
- Combination therapy
- Specialist referral

Selected severe cases may require low-dose opioid therapy administered under expert supervision (11,20).

Special populations

Pregnancy
Preferred interventions:

- Reassurance
- Iron replacement when indicated
- Sleep hygiene
- Physical activity

Pharmacological therapy is generally reserved for severe cases after specialist consultation (15).

Older Adults
Treatment considerations:

- Start with lower doses
- Monitor cognitive effects
- Minimize fall risk
- Review polypharmacy

Prognosis

The clinical course depends on the underlying aetiology.

Primary RLS

- Usually chronic
- Slowly progressive
- Characterized by periods of remission and relapse

Secondary RLS
May improve substantially when the underlying disorder is treated, particularly in cases related to:

- Iron deficiency
- Pregnancy
- Medication-induced symptoms

Conclusion

Restless Legs Syndrome is a common yet frequently under-recognized neurological disorder that significantly impacts sleep, quality of life, and daytime functioning. Diagnosis is clinical and based on the characteristic features of an urge to move the legs, worsening during rest, improvement with movement, and evening predominance. Primary care physicians should evaluate all patients for secondary causes, particularly iron deficiency, CKD, pregnancy, and medication-induced symptoms. Contemporary management emphasizes lifestyle measures, correction of iron deficiency, and pharmacologic treatment with α2δ calcium channel ligands or dopamine agonists when appropriate. Early identification and evidence-based treatment can lead to substantial improvements in patient outcomes and quality of life.

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