



# Restless Legs Syndrome

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## Introduction

Restless Legs Syndrome (RLS), also referred to as Willis-Ekbom disease, is a widespread and common sleep disorder where patients experience an overwhelming urge to move their legs. The symptoms occur predominantly while sleeping or at rest, often with painful and irritating leg sensations. Patients respond by moving their legs in an effort to relieve the sensations. Among the general population, Ohayon et al.'s recent review of the literature found that 5–8.8% of adults suffer from one of the different types of severities of RLS [1]. Half of those patients had only mild or infrequent symptoms, while nearly twice as many women suffer from RLS than men. Other associated comorbidities include depression, anxiety, and insomnia [1].

## Risk Factors

Numerous factors increase the risk for developing RLS. Iron deficiency, especially in elderly patients, remains a known risk factor, and iron supplementation can help reduce adverse symptoms in these cases [2]. Uremia due to end stage renal disease (ESRD) and chronic kidney disease (CKD) is another risk factor. RLS sometimes develops early in CKD, but more commonly occurs in ESRD [3]. Pregnancy also predisposes patients to RLS, developing in approximately 20% of pregnant females in first world countries [4]. In addition, RLS has been associated with several chronic conditions as congestive heart failure, diabetes mellitus, fibromyalgia and rheumatoid arthritis.

## Diagnosis

In 2012, the International Restless Legs Syndrome Study Group (IRLSSG) introduced new standards for the diagnosis of RLS, including a new fifth diagnostic criteria [5]. All five of the following conditions must be met to formally diagnose RLS. Firstly, patients must experience an inclination or urge to move their legs, usually associated with unpleasant feelings in the affected extremities. The urge to move is most commonly afflicts the lower limbs but in rare cases extends to the upper limbs. The unpleasant

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sensation is normally described as cramping, crawling, or a shock-like feeling. Secondly, the inclination to move must occur during periods of inactivity, such as lying down in bed. Thirdly, the impulse to move and any adverse feelings should be at least partially relieved by moving the limbs with activity such as walking or jogging. The fourth diagnostic criteria mandates that the condition and any accompanying ill-feelings are worse at night compared to the day. In severe cases of RLS, it may be difficult to decipher if the urge is more difficult at night. Finally, the first four criteria must not be the byproduct of another primary medical or psychiatric condition. The fifth requirement is new and implemented as a means of ruling similar diagnoses [5]. Again, all five criteria must be met for a clinician to diagnose RLS. When considering a diagnosis of RLS, clinicians should include in their work up a basic metabolic panel to assess kidney function, a complete blood count with peripheral smear, and an iron profile to check for iron deficiency.

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## Treatment

Treatment of RLS ranges over a broad spectrum of therapies depending on disease severity. Patients with mild disease can be treated with multiple types of behavioral therapy. Walking or any type of physical exercise can alleviate symptoms of mild RLS. Mentally stimulating activity, such as chess or crossword puzzles, has been shown to decrease the urge of RLS when at rest [2]. Many clinicians advise patients to cut down on caffeine and to quit smoking despite little evidence to support this recommendation. Alcohol consumption causes sleep cycle disturbances and may worsen RLS symptoms; consequently, alcohol cessation may decrease RLS symptoms [2]. Antihistamines, anti-nausea, and antiemetic drugs can exacerbate the urge symptoms of RLS, and patients should be advised to avoid these medications. Antidepressants such as tricyclic antidepressants, SSRIs, and SNRIs have been shown to exacerbate RLS symptoms,

but these medications should not be discontinued depending on the patient's mental state and depressive actions. Patients with serum ferritin levels less than 45 mcg should be treated with oral iron therapy, which is proven to decrease impulse and overall RLS symptoms in iron deficient patients [2].

Pharmacologic therapy remains the mainstay treatment of patients with moderate to severe RLS. Dopamine agonists such as ropinirole and pramipexole are first line therapies for RLS, and in fact were the first two FDA-approved medications indicated for moderate to severe RLS. Side effects of ropinirole and pramipexole are dose-related and include dizziness, hypotension, nausea, fatigue, and insomnia. These medications can aggravate impulse control disorders and should not be prescribed to patients with known impulse control disorders. Ropinirole is metabolized by the liver and is contraindicated in patients with liver failure, whereas pramipexole is metabolized by the kidney [2]. Rotigotine patches, a new dopaminergic medication, have demonstrated efficacy in treating RLS as a once daily 24 h patch. Adverse side effects of dopamine agonist therapy for RLS includes augmentation of symptoms. Augmentation generally occurs after months to years of dopaminergic therapy, with patients experiencing increases in symptom severity, frequency, and medication requirement [2]. The first non-dopaminergic medication approved to treat patients suffering from RLS was the anticonvulsant drug gabapentin. Some physicians consider gabapentin, as well as gabapentin enacarbil and pregabalin, a first line medication as it treats the neuropathy associated with RLS as well as the insomnia [2]. Patients who fail to respond to either dopamine agonists or anticonvulsants can use opioid medications as a last line therapy. Opioids can be used in concert with anticonvulsants and dopaminergic drugs in a multimodal strategy, or alone as a monotherapy. Pain specialists normally reserve treatment with methadone for patients with severe RLS that have failed all other therapies, as this opioid has demonstrated encouraging results for treatment refractory RLS [2].

## Differential Diagnosis

- Periodic limb movement of sleep.
- Rhythmic movement disorder. Characterized by specific type of movement when waking up and usually in children.
- Nocturnal leg cramps.
- Bruxism. Characterized by teeth grinding and jaw contractions.

### High Yield Points

- Restless Legs Syndrome (RLS) is sleep disorder that produces an urge or impulse to move one's legs, often accompanied by abnormal leg sensations.
- Iron deficiency is a risk factor for developing restless legs syndrome.
- Patients with mild RLS can be treated with behavioral therapy.
- Ropinirole and pramipexole are first line therapies for RLS.
- Side effects of ropinirole and pramipexole are dose-related and include dizziness, hypotension, nausea, fatigue, insomnia, and aggravation of impulse control disorders.

## Questions

1. Which of the following is NOT an adverse reaction of ropinirole?
  - A. Fatigue
  - B. Hypertension
  - C. Nausea
  - D. Dizziness

Answer: B
2. Which one of the following lab tests should be ordered when diagnosing Restless Legs Syndrome?
  - A. Hepatitis Panel
  - B. CSF 14–3–3 protein
  - C. Iron Profile
  - D. Alpha-fetoprotein

Answer: C
3. With medication is used to treat patients with severe RLS who have failed all other options?
  - A. Methadone
  - B. Gabapentin
  - C. Oxycodone
  - D. Rotigotine patch

Answer: A

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