

Treatment of Restless Legs Syndrome

Restless legs syndrome (RLS) is a neurological disorder characterized by dopamine deficiency resulting in discomfort in the legs and an irresistible urge to move them for temporary, symptomatic relief.¹ An estimated 10% of the US adult population have symptoms of RLS, although it may be under-diagnosed. In addition, RLS may be misdiagnosed as peripheral neuropathy, arterial or venous insufficiency, or leg cramps.² The most recent diagnostic criteria were updated in 2003; the presence of all four of the following is required to confirm RLS:³

- ◆ Urge to move the legs, usually accompanied by parasthesia
- ◆ Begins or worsens during rest or inactivity
- ◆ Partially or completely relieved by movement
- ◆ Circadian symptoms that worsen or only occur at night

RLS may be categorized based on symptom frequency:

- ◆ **Intermittent**-- severe enough to require treatment; not frequent enough for daily therapy
- ◆ **Daily**-- frequent and troublesome enough to require daily therapy
- ◆ **Refractory**-- inadequately controlled with appropriate drugs and adequate doses

Key Points

- ◆ The frequency of RLS symptoms should be assessed to determine appropriate pharmacologic treatment.
- ◆ Iron deficiency is a common secondary cause of and contributor to RLS and should be assessed initially and monitored regularly in all patients with symptoms.
- ◆ Ropinirole (Requip®) and pramipexole (Mirapex®) are first-line agents for patients with **daily** symptoms.
- ◆ Carbidopa/levodopa (Sinemet®) is considered the first-line agent for **intermittent** symptoms and should only be used **as needed** and no more than 3x/week in low doses (<50/200 mg) to avoid “augmentation.”
- ◆ “Augmentation” is defined as a worsening of symptoms and may include an earlier onset in the day and/or their spread to the upper extremities.⁴

Several non-pharmacologic therapies have been employed with success in controlling the symptoms of RLS, including abstaining from alcohol, nicotine, and caffeine. Other therapies include mentally alerting activities (crossword puzzles or video games), good sleep hygiene, hot baths, exercise, massage, and stretching.^{4,5} Iron status should be assessed and monitored in all patients regularly, and therapy should be initiated when serum ferritin is lower than 50 ng/mL.⁵

Dopaminergic agents are the cornerstone of RLS pharmacologic treatment. Patients with **intermittent** symptoms should be given a trial of carbidopa/levodopa (Sinemet®) to be used only when symptoms occur and no more than 3x/week. In addition, the recommended doses for RLS (<50/200 mg) are lower than those used in Parkinson’s disease. For patients with **daily** symptoms, dopamine agonists (Requip® or Mirapex®) are recommended first-line.^{4,5}

The dopamine agonists are generally well-tolerated, but have been shown to cause rare but serious adverse effects including sudden onset of sleep and compulsive behaviors (e.g gambling). Although rare, patients should be appropriately counseled and monitored regarding these adverse

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effects. For patients whose RLS symptoms are not controlled with a dopaminergic agent, anticonvulsants (e.g gabapentin), benzodiazepines, or opioids may be added or substituted. For refractory cases, a combination of these therapies or referral to a specialist may be necessary.^{4,5}

* Idaho Medicaid non-preferred; prior authorization required

1st Line Therapy for RLS		
Drug Class	Place in Therapy	Comments
Dopaminergic Agents Carbidopa/levodopa (Sinemet®)	Intermittent	Should only be used as needed and no more than 3x/week. If used more frequently, up to 70% experience “augmentation”- a worsening of symptoms or their development earlier in the day.
	Daily	FDA-approved for RLS. Should be taken daily at least 2 hours prior to symptom onset for maximum efficacy. Up to 25% of patients treated with a dopamine agonist experience “augmentation.”
	Ropinirole (generic, Requip®) Pramipexole (Mirapex®)*	
2nd Line/Adjunct Therapy for RLS		
Anticonvulsants	Daily	Gabapentin and carbamazepine have shown efficacy in treating RLS symptoms.
Benzodiazepines (BZD)	Intermittent or Daily	Clonazepam is the most studied BZD in RLS, but other BZDs are likewise beneficial. BZD agonists (zolpidem, zaleplon) can also be used to increase sleep quality.
Opioids	Intermittent or Daily	Low-moderate potency opioids (propoxyphene, codeine, hydrocodone) are often preferred over high-potency agents (oxycodone, methadone). The opioid-like drug, tramadol, can also be used.

Many medications are implicated in initiating or worsening symptoms of RLS. Although these drugs may be indicated, health care providers should be aware of this potential and use them cautiously in patients with RLS. Examples include dopamine-blocking agents such as antipsychotics, antiemetics, and metoclopramide. First-generation antihistamines may also aggravate the condition and are often used over-the-counter without the knowledge of the clinician. Antidepressants, especially the SSRIs, may likewise worsen RLS symptoms. Bupropion is preferred due to its stimulation of dopamine release.⁶

References

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