

Identification and Treatment of Restless Legs Syndrome

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Summary

Restless legs syndrome (RLS) is a prevalent but frequently under-diagnosed disorder. It can be a primary or secondary disorder that causes significant patient burden. Dopamine agonists are generally first-choice therapy. Ropinirole and pramipexole are effective, FDA-approved medications for RLS.

Key Points

- RLS occurs in about 10 percent of the population.
- Nonpharmacologic interventions may be beneficial.
- Approximately 3 percent of population will require treatment with medication.
- Secondary causes such as iron deficiency or medications have to be considered and managed.
- Dopamine agonists are first line therapy.
- Ropinirole and pramipexole are the only FDA-approved medications for RLS.
- Secondary therapies include levodopa, anticonvulsants, opioids, and benzodiazepines.

RESTLESS LEGS SYNDROME (RLS) IS VERY easy to diagnose. There are no objective tests for RLS. It is a purely clinical diagnosis based on historical information. Exhibit 1 lists the four main points of RLS.¹ There is an urge to move the legs which is often accompanied by some discomfort. The urge to move the legs worsens the longer someone is immobile. Moving around or massaging the legs relieves the sensations. Symptoms are worse at night and better during the day. Asking patients whether they have the urge to move their legs because they are uncomfortable at night will help identify patients with possible RLS.

Patients may complain of creepy, crawly, tingly, painful, burning, or achy sensations.² Patients make up their own terms to describe these sensations. Some describe this like worms or bugs crawling deep in the muscle or water running under the skin. If a patient states there is something wrong with their legs but they cannot describe it, they likely have RLS. The symptoms usually affect both legs simultaneously but can be unilateral or alternating. Occasionally, arms and even the whole body may be involved. Many patients experience symptoms daily.

RLS causes a significant burden. Discomfort and pain is a major cause of sleep disturbance. Most people present to a health care provider because of the sleep disturbance, not the pain or discomfort. They have trouble falling asleep, and decreased hours of sleep. This may lead to daytime fatigue and sleepiness. Reduced sleep also can lead to poor functioning at home or at work. Patients also have trouble sitting still at home and on the job because of restlessness. Because prolonged periods of sitting may provoke the symptoms, patients may have impaired social interactions. They may avoid situations where they have to sit, such as the movies, concerts, car trips, and airplane rides. RLS causes feelings of frustration, anxiety, depression, and embarrassment.

Unfortunately, this condition is frequently under-diagnosed. It can take patients many years and many providers to find the correct diagnosis. The differential diagnosis of RLS includes periodic limb movement disorder, peripheral neuropathy, nocturnal leg cramps, akathisia, vascular disease, and sleep disorders (e.g., sleep apnea or REM behavior disorder).

Because there is no objective measure for diagnosis,

**Exhibit 1: Restless Leg Syndrome (RLS):
Core Symptoms**

"URGE"

Urge to move limbs, usually accompanied or caused by an uncomfortable or unpleasant feeling in the limbs

Rest or inactivity precipitates or worsens symptoms

Getting up or moving improves the sensation

Evening or nighttime appearance or worsening of symptoms

*Acronym courtesy of Philip M. Becker, MD.
References: 1,2

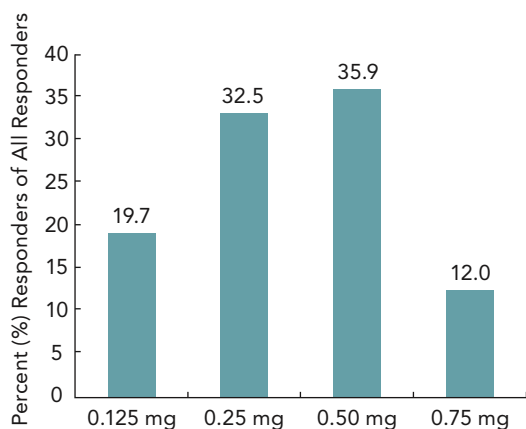
prevalence estimates depend on what question patients are asked. The overall prevalence of RLS is estimated at 10 percent of the general population.³⁻⁶ Of those with RLS, not all require treatment with medications. About 3 percent of the population is thought to require treatment. Up to 25 percent of primary care patients have RLS symptoms.⁷⁻⁸ The mean age of onset is 34, ± 20 years, but some patients have onset in childhood or young adulthood.^{9,10} These early onset patients tend to have a gradually progressive course.¹¹

In terms of pathophysiology, genetic factors are important. The main findings in terms of a genetic association come from two genome-wide association studies that have recently been reported. Both studies showed a very high association of RLS and periodic limb movements of sleep (PLMS, which occurs in patients with RLS) with BTBD9 gene on 6p and serum ferritin levels.^{14,15}

It is unknown where in the central nervous system

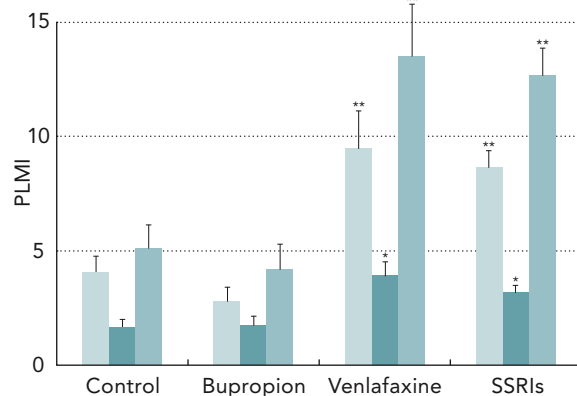
Exhibit 3: Effects of Pramipexole

Contribution of each pramipexole dose group (at week 6) to overall responder rates for IRLS



Reference: 29

Exhibit 2: SSRIs Increase PLM's



Reference: 23

the primary problem occurs. Iron status, dopamine pathways, and opioid pathways may play a role.^{12,13} There may be some interaction between these three different areas.

Serum ferritin levels negatively correlate with RLS symptoms.¹⁶ The lower the serum ferritin levels, the greater the symptoms. Indications are that there are low brain iron stores in patients with RLS. Iron may influence dopamine metabolism. Iron is a necessary cofactor for tyrosine hydroxylase, which is the rate-limiting enzyme in dopamine synthesis. Oral iron increases brain iron and improves symptoms of RLS in many patients.¹⁷ Therefore, RLS may involve a loss of iron homeostasis and dopamine regulation.

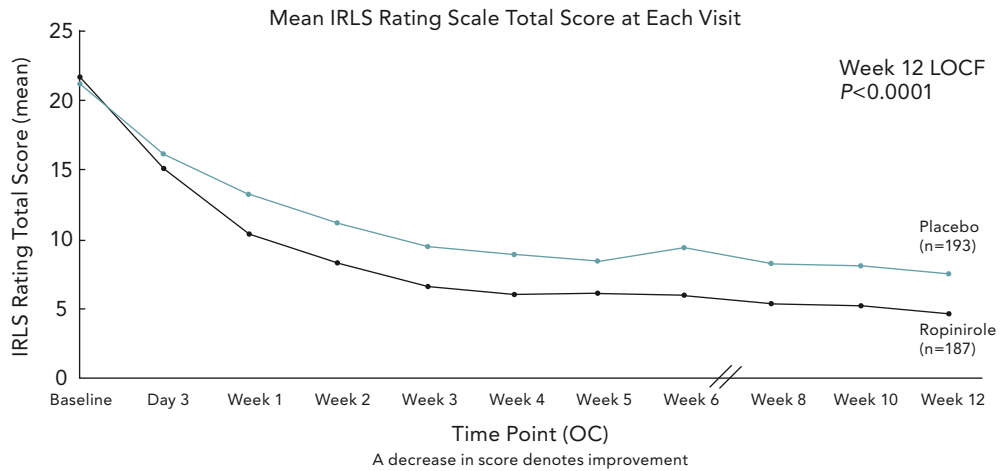
Additionally, there appear to be changes of dopamine binding in the brain and dopamine agonists improve RLS symptoms.¹⁸ There is an increased prevalence of RLS in patients with Parkinson's disease.¹⁹

Opioid receptors also are involved with RLS. It is hypothesized that there is hypofunction of the endogenous opioid system in RLS. Opioids will improve symptoms. Additionally, the administration of naloxone to opioid-treated patients exacerbates RLS symptoms and the administration of a dopamine receptor blocker antagonizes beneficial effects of an opioid on RLS symptoms.

Two major types of RLS occur – primary and secondary. Primary RLS accounts for the majority of cases. Secondary causes of RLS include iron-deficiency anemia (~25 percent of patients), pregnancy (~20 percent of pregnant women), end-stage renal disease/dialysis (up to 60 percent of patients), diabetes, rheumatoid arthritis, and peripheral neuropathy.²⁰

Medications (tricyclic antidepressants, selective

**Exhibit 4: Ropinirole Improved RLS Symptoms
Treat RLS US**



*P=0.003.
†P<0.001.
Reference: 35

serotonin reuptake inhibitors, monoamine oxidase inhibitors, lithium, antihistamines, and dopamine antagonists), smoking, caffeine, and alcohol also can precipitate RLS.²¹ In a population-based study of 18,980 individuals, the use of selective serotonin reuptake inhibitors (SSRIs) was demonstrated to be a risk factor for RLS (OR 3.11; 95 percent CI 1.66–5.79).³ Several studies have found an increase in periodic leg movement syndrome with the use of SSRIs (Exhibit 2).²² As noted in Exhibit 2, bupropion may be a better choice of antidepressant for use in patients with RLS because it has some dopaminergic activity.

The treatment strategies for RLS include discontinuing medications that can worsen RLS, nonpharmacologic treatments, and pharmacologic treatments. The main nonpharmacologic treatment is improvement of sleep hygiene with a standardized bedtime and wake time. Other interventions, which are supported by small, uncontrolled studies or anecdotal evidence, include moderate daytime exercise, reduced nighttime exercise, warm baths, thermal biofeedback, leg vibration/massage, acupuncture, and enhanced external counter pulsation (EECP). The medications that have been used include iron supplements, dopaminergic medications, anticonvulsants, opiates, and benzodiazepines.

Iron therapy should be considered if serum ferritin is less than 50 mcg/L or iron saturation is less than 16 percent.²³ A significant duration of iron supplementation might be required before symptoms decrease.

Dopamine agonists [pramipexole (Mirapex[®]), ropinirole (Requip[®])] are considered first-line treatment for RLS and are the only FDA approved

agents for RLS.²⁴ The majority of patients, even if iron deficient, will respond to dopaminergic agents. These agents can provide symptom relief in 70 percent to 100 percent of RLS patients, and reduce frequency of PLMS.

Levodopa, another dopamine agonist, provides dramatic and rapid control of symptoms in open-label and randomized controlled trials. It is one agent that may be effective in dialysis patients. Because it frequently causes augmentation and rebound, it is rarely used for chronic therapy. It can be given as needed before an event that is known to provoke symptoms (e.g., plane or car ride, theater). The most common adverse effects are nausea, dizziness, sleepiness.

Augmentation is a combination of earlier onset of RLS symptoms, increase of symptom severity, and involvement of other limbs.¹² A time shift of symptoms from bedtime to early evening, then to daytime, occurs. Augmentation is seen in up to 82 percent of RLS patients treated with levodopa.²⁵ Rebound is the wearing off of drug effect, typically in the morning. This is seen in up to 25 percent of RLS patients treated with levodopa.²⁵ Pramipexole and ropinirole can cause augmentation and rebound but to a lesser extent than levodopa.

Pramipexole's efficacy and safety has been studied in many open-label and double-blind trials.^{26–28} This agent is very effective for many patients at a much lower dose than what is required to treat Parkinson's disease. Exhibit 3 illustrates the effects of various doses of pramipexole on the mean International Restless Leg Syndrome (IRLS) score from one study.²⁹ The patients in this study have mean baseline IRLS scores of 25, which indicates severe RLS. The

most common adverse effects are nausea, orthostasis, sleepiness, and insomnia.

Ropinirole is the other agent FDA approved for RLS. This agent shows efficacy and safety similar to pramipexole.³⁰⁻³⁴ Again, it is effective in doses lower than those used to treat Parkinson's disease. Exhibit 4 presents data from one RLS study with ropinirole.³⁵ Because a subjective questionnaire is used, there is a significant placebo response in RLS medication studies. As noted in Exhibit 4, at every time point the IRLS score is significantly lower with active therapy. This agent causes nausea, vomiting, orthostasis, dizziness, sleepiness, and insomnia.

Anticonvulsants are considered second-line treatment. Although not FDA approved, gabapentin and carbamazepine are two of the agents that have been used. In small studies, these two agents are more effective than a placebo.³⁶ These agents have not been compared with dopaminergic agents, but are alternatives for patients who cannot tolerate the dopaminergic agents.

There is limited evidence that benzodiazepines are effective in RLS. Clonazepam is most commonly prescribed, but there are no good studies to support its use. It is primarily acting as a hypnotic rather than treating the underlying pathology. A benzodiazepine is an alternative for as needed use, but they do cause side effects.

Although opioids are effective, they are not typically used chronically for RLS. An opioid can be used as needed and may be the best agent to use in pregnancy. These agents are used when dopaminergic and anticonvulsant therapies are not effective, or cannot be taken and can be used in combination with other RLS meds. A recent small study examined the use of methadone for refractory RLS in 27 patients who failed dopaminergics.³⁷ All patients remaining on methadone for 23±12 months (n=17) reported at least a 75 percent reduction in symptoms, and none developed augmentation.

Two categories of patients require special considerations. Pregnant women should be checked for iron and folate deficiency. Folate deficiency appears to worsen RLS symptoms during pregnancy. No medications for RLS have an FDA category A status. Oxycodone and methadone are FDA category B. These opioids should be used with great caution, and treatment may be delayed until the last trimester of pregnancy.

For children, RLS is typically misdiagnosed. Children may not complain of pain but will have restlessness. RLS may be diagnosed as "growing pains" or attention deficit hyperactivity disorder (ADHD). There are limited trials using levodopa and pergolide in children. The dopamine agonists should not be used in pregnant women or children.

Conclusion

RLS is a highly prevalent disorder. It should be suspected in any patient with leg discomfort in the evening or when in bed. Although it is easily diagnosed, it is often under-recognized by health care providers. Secondary causes such as iron deficiency have to be considered and managed. Dopamine agonists are generally first-choice therapy. Ropinirole and pramipexole are the only FDA approved medications for RLS. Secondary therapies include levodopa, anticonvulsants, opioids, and benzodiazepines. **JMCM**

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