

# Restless Legs Syndrome

Here's what you  
need to know about  
RLS.

BY RAJAT K. LAHIRI, DPM AND G. DOCK DOCKERY, DPM

## Goals and Objectives

- To improve the recognition of restless legs syndrome (RLS) as a clinical entity and to review the current recommendations for treatments of this condition.
- To review and learn specific findings of the International Restless Legs Syndrome Study Group (IRLSSG) regarding this condition.
- To provide additional understanding of the history and epidemiology of restless legs syndrome and its differential diagnosis.
- To better understand current adjunctive and complementary treatment options for the management of restless legs syndrome.

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Following this article, an answer sheet and full set of instructions are provided (pg. 96).—**Editor**

## Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom Disease, is a neurological disorder that can significantly affect one's life. Simply said, it is a disorder that creates an urge to move one's legs and creates an uncomfortable feeling until said movement occurs. Symptoms usually occur in the late evening hours and are most severe at night when a person is resting. Additionally, symptoms may occur after there is prolonged inactivity or after sitting for extended periods of time. Moving the legs or getting up and walking will temporarily relieve the sensations, but they re-

turn once the movement stops. While it may seem simple at its core, it can create great disturbances in day-to-day life affecting sleep, mood, and energy levels throughout the day.

## History

According to Coccagna G, et al., the first description of RLS was made in 1685 by one half of the eponym of which the disease is also known as (Willis-Ekbom Disease): English physician Thomas Willis wrote: "Wherefore to some, when being abed they betake themselves to sleep, presently in the arms and legs, leapings and contractions of the tendons, and so great a

restlessness and tossing of their members ensue, that the diseased are no more able to sleep, than if they were in a place of the greatest torture".<sup>1</sup> This quote alludes to the fact that sleep is most affected in these patients, primarily due to the neurological takeover of involuntary movements.

The other half of the name Willis-Ekbom Disease is from Karl-Axel Ekbom, a Swedish neurologist, who was the first to use the term "Restless Legs Syndrome" and he published his findings on 34 patients in 1944 and concluded that there was a vascular cause to this condition, and recom-

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mended vasodilators as the first-line therapy.<sup>1,3</sup> What was interesting is that Willis' original interpretation of this condition involved both upper and lower extremities, yet the term Restless Legs Syndrome singles out the lower extremities. After Ekbohm's account in 1944, in Europe, this condition came to be known as Ekbohm's Disease.

Around 1947 in France, Bonduelle and Jolivet published on RLS suggesting the etiology as "a circulatory disturbance in the lumbar spine consisting in slowing of venous flow".<sup>1</sup> In 1962, Menninger-Lerchenthal concluded that RLS was an extrapyramidal disease caused by an iron metabolism disorder as they found low iron blood levels to be common in these patients. Further in 1962, Coccagna and associates noted that these involuntary kicking movements occur during sleep.<sup>1</sup> While through-

out history many postulations were made on the cause of RLS, it is a condition that is still under investigation and affects many people worldwide.

**Epidemiology**

An epidemiology literature review on RLS done by Ohayon, et al., noted that from 2000 to 2012 at the time of

15%.<sup>3</sup> When evaluating prevalence based on meeting the IRLSSG (International Restless Legs Syndrome Study Group) Criteria, studies report a prevalence between 5.0% and 14.3%.<sup>3</sup>

In terms of gender, the majority of studies indicate a higher prevalence among women than in men, with many studies showing preva-

**The majority of studies indicate a higher prevalence of RLS among women than in men.**

publication, 47 epidemiological studies were published on RLS. Before 2000, only one paper was published on this topic. They noted that in recent years, there has been an increase in articles, and this may in part be due to the increased awareness and prevalence of this condition. When looking at RLS as a solitary condition, prevalence was reported between 9.4% and

lence being double that in women than men. RLS is also interestingly the most common movement disorder during pregnancy and can be as prevalent as 19.5%. Bonduelle and Jolivet, as described earlier associated pregnancy and the slowing of venous flow as the reason for this phenomenon. Per this epidemiologic review by Ohayon et al, there was no consensus among studies on the age demographics of RLS, but many results reported that "most individuals suffering from RLS are over age of 40 but it can start at any age."<sup>3</sup> Additionally, some medicines may worsen symptoms of RLS. These include some antidepressants, some antipsychotic medicines, some anti-nausea medicines, and some cold and allergy medicines.<sup>4</sup>

**Clinical Presentation**

At its core, RLS clinically presents as a sensation in the lower extremities that causes an uncontrollable urge in patients and these sensations cause patients to move their legs. These sensations are triggered by long moments of rest, whether it be during sleep or general periods of inactivity. The sensations are usually relieved by movement but restart when movement is ceased. Often, RLS is categorized as a sleep disorder as this sensation is common during sleep, and the movement that satiates this sensation often wake the patients and makes it hard for them to fall back asleep.<sup>1</sup>

**Diagnostic Criteria**

The diagnosis for RLS is a clinical one based on patient symptoms and experiences. In 2003 at the National

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**Table 1<sup>4</sup>**  
**IRLSSG Diagnostic Criteria**  
*(all must be met)*

- 1** An urge to move the legs, usually, but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.
- 2** The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
- 3** The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- 4** The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day
- 5** The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

*International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria for restless legs syndrome/Willis-Ekbohm disease (RLS/WED)*

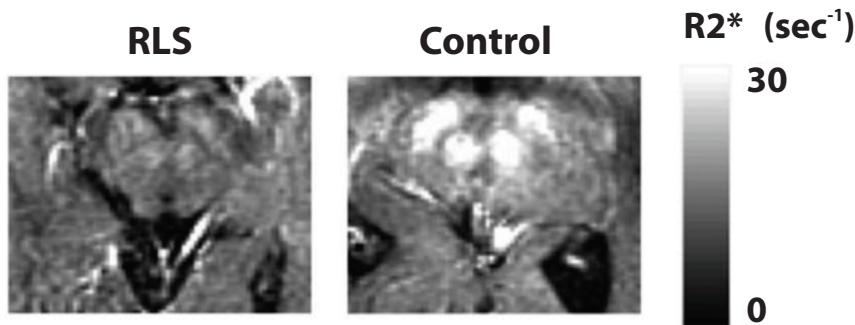


Figure 1<sup>5</sup>: In RLS, brain dopamine is at increased levels, which causes a post-synaptic down-regulation causing a decrease in dopamine-2 receptors.

From: Allen RP, Barker PB, et al. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology*. 2001;56:263-265

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Institutes of Health, a large international body of RLS research experts formed an International Restless Legs Syndrome Study Group (IRLSSG), and this group developed a consensus criterion. This diagnostic criterion

**Pathophysiology**

Dr. R. P. Allen from Johns Hopkins University, a prominent researcher on RLS, describes three pillars that underly the pathophysiology of RLS: “genetics, iron/dopamine, cortical-spinal excitability”.<sup>4,5</sup> In terms of genetics, as other studies have indicated some level

the substantia nigra and red nucleus of RLS patients.<sup>5,7</sup> This iron deficiency is said to stem from the mechanism of “a failure to provide adequate iron transport across the blood-brain barrier compounded by a regional failure to import adequate iron into critical neuronal cells”.

The iron deficiency pillar of RLS has been researched and thought to physiologically cause hypoxia and myelin loss.<sup>5</sup> These same studies have shown leg muscle hypoxia in RLS patients, which provides a connection to the impact of iron deficiency in this condition. In a study by Conner, et al., postmortem analyses of RLS patients found a 25% decrease in myelin proteins.<sup>8</sup> Myelin synthesis is directly affected by iron stores in the brain. With myelin loss, a patient’s sensorimotor integration is significantly impacted, leading to the clinical presentation of much of RLS.

RLS pathophysiology is often linked to dopamine pathways and imbalance.<sup>1,4,5</sup> The mechanism is explained as such. In RLS, brain dopamine is at increased levels, which causes a post-synaptic down-regulation causing a decrease in dopamine-2 receptors,<sup>5</sup> as seen in Figure 1.

As dopamine levels follow a circadian pattern where they decrease in the evening, these lower levels in the evening with the decrease in receptors causes an inappropriate balance, lending credence to the idea that RLS symptoms mostly occur at night.

While the expected initial intuitive thought regarding treatment is

**Patients with RLS have periodic leg movements that occur in sleep and usually last for 10-90 seconds.**

was developed over many years, and in 2012, they published an updated diagnostic criteria with 5 criteria as seen in Table 1.<sup>4</sup>

The IRLSSG also documents specific features that can help support the diagnosis of RLS. They note that patients with RLS have periodic leg movements that occur in sleep and usually last 10-90 seconds. Another feature that can support diagnosis of RLS is dopaminergic treatment response. They state that “failure ever to respond to dopaminergic treatment should raise some concern about the accuracy of diagnosis, but it does not preclude a diagnosis of RLS/WED.”

The working group also found a significant genetic involvement to RLS, where one study showed 20% of RLS patients reported RLS among first-degree relatives. The last feature that can support this diagnosis is counterintuitive: “lack of expected daytime sleepiness”. These patients can experience other factors related to lack of nighttime sleep such as fatigue and depression; however, they usually do not feel sleepy during the day.<sup>4</sup>

of genetic concordance,<sup>4</sup> other genome studies have shown 5 specific genomic regions that are risk alleles on chromosome 2, independent of decreased iron stores. However, as noted by Allen, this is preliminary information that has the potential for future treatments; currently, however, there is a lack of understanding re: how to best use this information on these risk allelic regions.<sup>5</sup>

**The first step in the treatment algorithm is to test iron levels.**

Restless legs syndrome has a common factor that is popularly thought to be a predominant cause: iron deficiency.<sup>1,3-5</sup> The thought in most literature is that the decrease in peripheral iron stores is a major factor in increase of RLS. Newer studies have shown that RLS has more to do with central nervous system iron stores rather than peripheral ones.<sup>5</sup> Based on MRI findings, multiple studies have confirmed that there is decreased brain iron in

to increase dopamine levels at night, this would lead to further desensitization and worsening of RLS. Some authors mention the use of longer-acting medications such as rotigotine, to reduce the rate of desensitization.<sup>5</sup>

The last pillar in the pathophysiology of RLS as mentioned by Allen is cortical excitability. In RLS, there is increased cortical excitability and a decreased threshold for motor re-

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sponse with stimulation.<sup>5</sup> There are limited studies on this neurological mechanism; however, some studies have shown this excitability is decreased with dopamine treatment.<sup>9,10</sup>

**Treatment**

The first step in deciding treatment is differentiating between the presence of idiopathic RLS or secondary RLS due to another cause such as iron deficiency, pregnancy, or medication effect.

One of the most common factors of RLS is iron deficiency.<sup>1,2</sup> The IRLSSG published a task force report on the treatment of secondary RLS due to iron deficiency. They recommend for adults with a serum ferritin > 300 micro-

grams/l, be given IV Ferric carboxymaltose as a first-line treatment. For adults with serum ferritin < 75 micrograms/l, oral iron 65 mg is effective.<sup>12</sup>

Another line of therapy often mentioned is the use of dopaminergic agents. However, due to the dopaminergic imbalance in RLS, dopaminergic agents can often worsen symptoms due to downregulation. Hence, the IRLSSG recommends minimizing exposure to these agents.<sup>4,11,12</sup> Rather, they recommend a reasonable first-line treatment being gabapentin enacarbil 600mg at 5 PM, gabapentin 300mg at night, or pregabalin 75mg at night, titrating up to 300mg at night, and if unsuccessful, adjunct with a dopamine agonist (levodopa). However, levodopa should be avoided in chronic patients, hence the inverse statement also holds true, where levodopa can help patients who have infrequent symptoms. Most medicines prescribed for RLS are not recommended in pregnancy.

In terms of nonpharmacological treatment options, some studies have shown 30 minutes of aerobic and lower body resistance training exercises 3 days per week improves symptoms of RLS.<sup>11,14</sup> Other strategies described in literature include various transcranial stimulations with magnetic

fields, temperature, or tactile sources.

Other recommendations to help alleviate symptoms of RLS include:

- Warm baths. Soaking in a warm bath for 20 minutes or more may relax muscles.
- Warm or cool packs. The use of heat or cold packs on the calves, or alternating the use of the two, may lessen leg symptoms.
- Sleep hygiene. Create a quiet, cool sleeping area. Get in a routine of going to bed and rising at the same time each night.
- Avoid caffeine and other stimulants. Avoid caffeine-containing products like coffee, tea, soda, and chocolate for a few weeks to see if this helps in getting better sleep.
- Lower leg compression wraps

gabalin. As mentioned earlier, dopamine agonists should be avoided, but can be used as second-line treatment; however, augmentation and desensitization must be monitored.<sup>11,13</sup>

For refractory RLS, combination therapy is recommended with two agents including any of a dopamine agonist, alpha-2 delta ligand, opioid, or benzodiazepine, with the idea of reducing dosage of either agent. An alternative treatment that is suggested is opioid monotherapy which has shown to help some patients alone. However, the current anti-opioid climate may make these medications difficult to use. In severe refractory RLS resistant to other treatments, consider methadone.<sup>13</sup>

**Conclusion**

As described in this article, RLS affects a significant portion of the population, and has multiple causes and factors, while also having multiple lines of treatments with various efficacies. Over the past two decades, research on RLS has increased and studies continue to tout new treatments.<sup>3,14</sup> Future directions and studies may give us more insight into the role of other nonpharmacological treatments such as mechanical devices and other forms of electrical stimulation.<sup>14</sup> As new research is done on alternative therapies that have less side effects, the management strategies of RLS are likely to continue to evolve.<sup>16</sup> **PM**

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## Compression wraps, warm baths, and aerobic exercise are non-pharmaceutical treatments for RLS.

or vibrating pads. A lower leg compression wrap will apply pressure to the leg and foot and may help relieve the symptoms. Using an electric pad that vibrates on the back of the legs may also help.

**Treatment Algorithm**

Silber, et al., from the Center for Sleep Medicine at the Mayo Clinic published an updated evidence-based algorithm for the treatment of RLS.<sup>13</sup>

The first step towards treatment is to check the iron status of all patients with RLS and treat accordingly with IV versus oral iron as described in detail in the previous section. Another consideration is to work up any potential causes such as sleep disorders or medication effects.<sup>13</sup>

The Mayo Clinic algorithm is then split into intermittent RLS, chronic persistent RLS, and refractory RLS. For intermittent RLS, the recommendations are to trial caffeine and alcohol abstinence, and consider intermittent use of carbidopa/levodopa, low potency opioids (codeine or tramadol), or benzodiazepine agonists.

For chronic persistent RLS, the first line treatment is alpha-2-delta calcium channel ligands such as gabapentin enacarbil, gabapentin, or pre-



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## CME EXAMINATION

**SEE ANSWER SHEET ON PAGE 97.**

**1) Of the following, which is true in regard to the demographics of people with RLS?**

- A) Most individuals are less than age of 40
- B) Pregnant individuals do not get RLS
- C) Females are affected more than males
- D) Prevalence is less than 1%

**2) Which medications can worsen the effects of RLS?**

- A) Anti-nausea
- B) Anti-psychotic
- C) Anti-depressants
- D) All of the above

**3) Patients with RLS have periodic leg movements that occur in sleep and usually last for how long?**

- A) 1-5 seconds
- B) 10-90 seconds
- C) 120-180 seconds
- D) 5 minutes

**4) Which of these items underly the pathophysiology of RLS?**

- A) Iron and dopamine levels
- B) Genetics
- C) Cortical-spinal excitability
- D) All of the above

**5) Which of the following is true in patients with RLS?**

- A) Decrease in brain iron levels
- B) Increase in myelin proteins
- C) Adequate oxygenation of leg muscles
- D) Brain tumors

**6) What lab test is used to dictate the type of iron supplementation used for treatment in RLS?**

- A) Serum dopamine
- B) Urine iron
- C) Serum ferritin
- D) Creatinine

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**7) Which of these non-pharmacological treatments is NOT indicated for RLS?**

- A) Compression wraps
- B) Warm baths
- C) Aerobic exercise
- D) Caffeine

**8) In the treatment algorithm for RLS, what is the first step?**

- A) Nerve conduction studies
- B) Sleep study
- C) Check iron levels
- D) Perform Brain MRI

**9) For chronic RLS, what is a reasonable first-line treatment?**

- A) Gabapentin
- B) Methadone
- C) Levodopa
- D) Midazolam

**10) Which of the following statements is true?**

- A) Symptoms of RLS are worse during the day
- B) Symptoms are partially relieved with movements
- C) Brain dopamine levels are low in RLS
- D) There is no genetic involvement to RLS

**SEE ANSWER SHEET ON PAGE 97.**

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**(Lahiri and Dockery)**

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