The Restless Legs Syndrome Foundation started in 1989 when eight individuals with restless legs syndrome (RLS) began sharing letters and discussing their “rare” condition. In 1992, the Foundation was incorporated as a non-profit organization to address the growing need for research and information about this unknown condition. In the beginning, the Board of Directors would gather around the kitchen table of Executive Director Pickett Guthrie to discuss their experiences with the disease and what courses of action would provide the most relief for those with RLS. Their goals were simple and yet groundbreaking: increase awareness, improve treatments, and, through research, find a cure.

For more information on RLS, the Foundation, and how to become a member, visit our website at www.rls.org.

This publication has been reviewed and approved by our Scientific and Medical Advisory Board. Literature distributed by the Restless Legs Syndrome Foundation, including this Bulletin, is offered for informational purposes and should not be considered as a substitute for the advice of a healthcare provider. As always, individuals suspecting they may have RLS should consult a qualified healthcare provider.
Restless Legs Syndrome: Diagnosis and Treatment in Primary Care

Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a sensorimotor disorder characterized by a distressing urge to move the legs and, in some cases, other parts of the body such as the arms. This urge is usually accompanied by sensory disturbances ranging from discomfort to pain in the affected parts. RLS symptoms most often begin during rest or inactivity and can be relieved or suppressed by movement. RLS follows a circadian pattern with symptoms most intense and most easily provoked in the evening and nighttime hours. RLS symptoms can range from relatively mild to severe, from only rarely experienced, to an intense daily torture. When severe, RLS may have profoundly disruptive effects on sleep quality, quantity and daily life.

Prevalence

RLS affects 5 to 10 percent of adults in European countries and other countries whose populations originated largely in Europe. Studies in Western Europe and the United States using conservative criteria of individuals with moderately or severely distressing RLS symptoms occurring at least twice a week yielded a prevalence of 1.5 to 4.4 percent.

In the United States, RLS is believed to affect more than 10 million adults and an estimated 1.5 million children and adolescents. About one-third of those with RLS symptoms are bothered sufficiently enough to seek medical attention. Women seem more susceptible to RLS than men, and most studies find that women are at least twice as likely to have RLS than men. RLS is more common in older adults, although it can occur as early as the preschool years. However, some studies have suggested that the frequency of RLS may decrease in the elderly.

Etiology

RLS is believed to be a disorder of the central nervous system. It is not caused by psychiatric disorders nor by stress, but these conditions may contribute to or exacerbate RLS. There is a high frequency of familial cases of RLS consistent with a genetic origin in primary RLS. The condition seems to have a complex genetic basis, but environmental factors appear to be equally important in provoking RLS. There have been major genetic advances in the study of RLS. Between 2001 and 2008, six different linkages (RLS1-RLS6) were reported. In July 2007, two groups, both working in multiple populations using genome-wide associations studies, reported that several natural variants in two different genes were associated with the risk of developing RLS. Since then, several more variants have been identified, adding three more genes to the list of RLS-risk genes. The overall risk of developing RLS for a person who has one or more of these genes is still small, indicating that more genes have yet to be identified, or other genetic or environmental factors are involved. So far, it has not been possible to determine the link between the natural variants in the gene structure and the biological determinations of RLS.

Future research into the normal function of these genes is likely to help us understand how these genes lead to the development of RLS. One major theory of RLS causation is that a deficiency in brain iron, particularly within dopamine-containing neurons, may predispose a person to RLS. A link between one of the genetic associations and body iron stores suggests that iron metabolism may be one of the pathways influenced by genetic factors favoring development of RLS. In a current model of causation, brain iron deficiency leads to a dysfunction of the dopamine pathways where abnormal function may cause the symptoms of RLS. As far as we know, RLS is neither a structural nor a neurodegenerative disorder, and most individuals with RLS are neurologically normal except for their RLS. Despite their definite response to dopaminergic medications, RLS and Parkinson’s disease seem to have very different underlying biologies and there is no evidence that RLS can lead to Parkinson’s disease. The etiopathogenesis of RLS at this point is largely unclear and there is more research that needs to be done to clarify this.

Presentation

Individuals who have RLS may not articulate their signs and symptoms. Healthcare providers should be alert to possible RLS in individuals who complain of nocturnal leg discomfort or sleep disruption. An individual’s description of their uncomfortable sensations will often vary. However, common phrases used to describe the sensations are described in Table 1. The key element is the urge or need to move, although some individuals will emphasize specific sensory symptoms.

<table>
<thead>
<tr>
<th>Table 1. Phrases patients use to describe RLS sensations</th>
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<tbody>
<tr>
<td>“It just makes me want to move.”</td>
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<tr>
<td>“It feels like I have water running underneath my skin.”</td>
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<tr>
<td>“It feels painful.”</td>
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<tr>
<td>“It burns and aches.”</td>
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<tr>
<td>“It feels like I have a toothache in my leg.”</td>
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<tr>
<td>“I have the heebie jeebies in my legs.”</td>
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<tr>
<td>“My legs feel creepy, crawly, and tingly.”</td>
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<tr>
<td>“It feels like I have worms or bugs crawling deep in my muscles.”</td>
</tr>
<tr>
<td>“It feels like electricity in my legs.”</td>
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</table>
Individuals with RLS are often unable to ride comfortably in a car or airplane for long periods of time, they can have difficulty falling or staying asleep, and they often suffer from fatigue, lack of concentration, or a depressed mood during the day.10-14

**Diagnosis**

A diagnosis of RLS is based primarily upon the clinical interview with the patient. Currently, there are no lab tests that can definitively confirm or deny the presence of RLS. The use of sleep studies or a suggested immobilization test15 may occasionally be helpful in difficult cases by demonstrating the presence of periodic limb movements of wake and/or sleep.16 It has been proposed that response to a dopaminergic medication can be formalized as a confirmatory diagnostic test.18 A structured interview has been used in various research projects.19

**RLS Primary Diagnostic Criteria**

Since 2003, there have been four required primary diagnostic criteria needed to support a diagnosis of RLS:

- **Urge to move the legs that is irresistible.** Sometimes the arms or other body parts are involved in addition to the legs.

- **Onset or exacerbation with rest.** The motor and sensory symptoms most often begin or worsen during periods of rest or inactivity, particularly when lying down or sitting. Rest includes both lack of motor activity and decreased mental activation.

- **Relief with movement.** RLS symptoms are partially or totally relieved by movements such as walking or stretching; symptoms are relieved for at least as long as the activity continues. Mental activation also reduces symptoms.

- **Circadian pattern.** RLS symptoms usually occur or worsen in the evening or at bedtime. Symptoms are usually dormant in the morning.

In 2014, the 3rd edition of the International Classification of Sleep Disorders also published revised RLS diagnostic criteria.48 These criteria are very similar to those set forth by the IRLSSG, again stressing differential diagnosis and clinical significance, although unlike IRLSSG criteria, there was no subdivision of RLS symptom severity into chronic or intermittent. The American Psychiatric Association set forth yet another set of RLS diagnostic criteria in its 5th edition of the Diagnostic and Statistical Manual of Psychiatric Disorders.49 These criteria stressed the need to have RLS symptoms at least three times weekly and at least for three months, while keeping the original four necessary criteria of RLS.

**Supportive Clinical Features**

There are also some supportive clinical features whose presence, while not essential to a diagnosis of RLS, can help support the diagnosis (Table 4):

- **Positive family history.** The frequency of RLS among first-degree relatives of individuals with RLS is 3 to 7 times greater than in individuals without RLS.20,21

- **Positive response to dopaminergic therapy.** Up to 90 percent of patients with RLS show at least an initial positive therapeutic response to either L-dopa or dopamine-receptor agonists. Dosages for RLS are considerably lower than those prescribed in the treatment of Parkinson’s disease.18,22,23

- **Presence of periodic limb movements (PLM).** These movements, which occur in about 80 percent of individuals with RLS, can help confirm a diagnosis.16,24 However, because PLM, especially those with periodic limb movements in sleep (PLMS), are also common in some other disorders and among the elderly, this finding is not specific.25 Genetic studies suggest that there may be a strong genetic connection between PLM and RLS.7 When sleep complaints are associated with PLMS without RLS or any other cause for the complaints, a diagnosis of periodic limb movement disorder (PLMD)26 can be made.
### Table 3. International RLS Study Group Consensus Diagnostic Criteria for RLS

#### Essential 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.\(^a,b\)

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.\(^c\)

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.\(^d\)

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).\(^e\)

#### Specifiers for clinical course of RLS:\(^f\)

- A. Chronic-persistent RLS: symptoms when not treated would occur on average at least twice weekly for the past year.

- B. Intermittent RLS: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

#### Specifier for clinical significance of RLS:

The symptoms of RLS cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

- a. Sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs.

- b. For children, the description of these symptoms may vary based upon the child’s own words.

- c. When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.

- d. When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.

- e. These conditions, often referred to as “RLS mimics,” have been commonly confused with RLS particularly in surveys because they produce symptoms that meet or at least come very close to meeting criteria 1–4. The list above gives some examples that have been noted as particularly significant in epidemiological studies and clinical practice. RLS may also occur with any of these conditions, but the RLS symptoms will then differ in degree, conditions of expression or character than those usually occurring as part of the other condition.

- f. The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS such as pregnancy or drug-induced RLS where the frequency may be high but limited to duration of the provocative condition.
In addition to the supportive clinical features mentioned above, other associated features can help direct a person’s diagnosis:

- **Clinical course.** The clinical course of RLS varies considerably, but it is generally chronic and progressive in most individuals. Onset of RLS in individuals younger than age 30 tends to be more insidious and may not become troublesome until middle or later age. When the age of onset is 50 years or older, symptoms often appear more abruptly. In some individuals, RLS can be intermittent and may remit spontaneously for many years.

- **Sleep disturbance.** Disturbed sleep is a common morbidity for RLS and deserves special consideration in planning treatment. Sleep disturbance is often the primary reason a person seeks medical attention. A sleep study is not needed to diagnose RLS, but if done may show delayed sleep latency, excessive PLM, and disrupted sleep. A person with moderate to severe RLS may average less than five hours of sleep per night and may be more sleep deprived on a chronic basis than individuals with almost any other persistent disorder of sleep. For individuals with mild RLS, sleep disturbance may not be a problem or may be a less significant issue.

- **Normal neurological exam.** The neurological exam is normal in primary idiopathic RLS. RLS sometimes co-occurs with peripheral neuropathy, Parkinson’s disease, or multiple sclerosis. There may be abnormal exam findings associated with these entities.

**History and Physical Examination**
A history is directed towards determining if the person meets the primary diagnostic criteria (Table 2) and to rule out other disorders that share features of RLS.

### Table 4. Supportive clinical features and associated features

<table>
<thead>
<tr>
<th>Supportive Clinical Features</th>
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<tbody>
<tr>
<td>• Positive family history</td>
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<td>• Positive response to dopaminergic therapy</td>
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<tr>
<td>• Presence of periodic limb movements (PLM)</td>
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<table>
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<tr>
<th>Associated Features</th>
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<tbody>
<tr>
<td>• Clinical course is generally chronic and progressive</td>
</tr>
<tr>
<td>• Sleep disturbance</td>
</tr>
<tr>
<td>• Normal neurological exam in primary RLS, unless a co-morbid condition exists</td>
</tr>
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### Table 5. Differential diagnosis of RLS

<table>
<thead>
<tr>
<th>Disorders of Restlessness</th>
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<tr>
<td>• Neuroleptic-induced akathisia</td>
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<td>• Fidgets</td>
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<tr>
<td>• Semiconscious leg jiggling or habitual foot tapping</td>
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<tr>
<td>• Involuntary leg movements (PLM, propriospinal myoclonus at sleep onset, rhythmic movement disorder)</td>
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<tr>
<th>Disorders of Leg Discomfort</th>
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<tbody>
<tr>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td>• Nocturnal leg cramps</td>
</tr>
<tr>
<td>• Vascular or neurogenic claudication</td>
</tr>
<tr>
<td>• Pruritis</td>
</tr>
<tr>
<td>• Arthritic leg discomfort</td>
</tr>
<tr>
<td>• Painful myopathies</td>
</tr>
<tr>
<td>• Varicose veins or venous insufficiency</td>
</tr>
<tr>
<td>• Deep vein thrombosis</td>
</tr>
<tr>
<td>• Fasciculations</td>
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<tr>
<td>• Fibromyalgia</td>
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</table>

<table>
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<tr>
<th>Disorders of Both Restlessness and Leg Discomfort</th>
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<tbody>
<tr>
<td>• Positional discomfort (resolved by changing position, not walking)</td>
</tr>
<tr>
<td>• Painful legs and moving toes</td>
</tr>
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</table>

### Differential Diagnosis
Other disorders that may share some of the features of RLS, and must be ruled out, are listed in Table 5. Two types of conditions are most likely to be confused with RLS: those which involve restlessness, and those which include leg discomfort. These conditions, which can meet some of the diagnostic criteria for RLS, have been called mimics. It is also possible that RLS can coexist with other certain disorders, such as diabetic neuropathy, for example. At times it may be challenging to differentiate RLS from comorbid disorders. Close questioning of the person may reveal differences in the quality of dysesthesia or in the time of day for symptom presentation. Clarification of primary diagnosis may be accomplished with the “L-dopa test” in that the disorders that mimic RLS do not typically show response to dopaminergic therapy.
however, it is not sufficient to test joint position sense and not vibration, as the latter test is more sensitive in detecting a peripheral nerve problem. Nerve damage may also lead to reports of painful sensations of burning or electric-like shocks.

Sometimes the painful sensations of peripheral neuropathy are similar to those of RLS. Moreover, the two disorders share many common risk factors including diabetes and renal disease. RLS may occur with or be triggered by neuropathy, but when RLS and neuropathy occur together, efforts should be made to distinguish which symptoms are from RLS and which are from the neuropathy because treatments may vary. The general medical exam should focus on looking for signs of arthritis, arterial or venous disease, or other forms of local trauma of the legs. Dorsalis pedis and posterior tibialis pulses should be felt. Temperature, color, and texture of the feet should be noted. RLS is usually inactive during examination in the morning or early afternoon, and the leg is not normally discolored, swollen, or tender. Strength and movement should be normal. Examination in the afternoon or evening may reveal periodic movements, primarily of the feet or lower extremity, as the person sits quietly on the examination table.

**Laboratory Evaluation**

There are no laboratory findings diagnostic of RLS. All patients with RLS should have an assessment of their iron stores. The iron study should include serum iron, ferritin, TIBC and percent transferrin saturation. The blood should be drawn in the early morning before 9 am, following an overnight fast (no eating or drinking after midnight). Also avoid a heavy meat meal the night before. The current recommendations, based solely on oral iron treatment, limits treatment to those with a serum ferritin level less than 75 mcg/L. However, two recent randomized, controlled trials of IV iron therapy in non-anemic RLS patients with a ferritin level less than 300 mcg/L, demonstrated significant treatment benefits. However, ferritin is not always a reliable measure because it can increase significantly with inflammation or infection (even a simple cold) and remain elevated even 6 weeks after the inflammation or infection subsides. Fasting serum iron less than 60 µg/dl, percent transferrin saturation less than 18 or a TIBC greater than 400 would suggest the presence of an iron deficiency even if there is no indication of an anemia. Other laboratory tests are generally not needed unless there is clinical suspicion of associated conditions such as a peripheral neuropathy (when glucose and other studies may be indicated) or chronic renal failure. While a sleep study is not indicated for diagnosis of uncomplicated RLS, suspicion of additional sleep problems, such as respiratory problems (obstructive sleep apnea, for example) or sleep-related violent behavior, may suggest the need for polysomnography. Electrodiagnostic tests of nerve function are only indicated for individuals with clinical suspicion of peripheral neuropathy or radiculopathy. The suggested immobilization test (SIT) is a provocative test in which the person tries to remain still while seated in bed for about an hour, preferably in the evening when RLS symptoms are most intense. The degree of discomfort is periodically monitored and the number of PLM is measured. The test is uncomfortable and has only moderate sensitivity and specificity for the diagnosis of RLS. For research purposes, a multiple SIT test that provided four trials at two-hour intervals between 6:00 pm and midnight showed clinically relevant validity in individuals with RLS with or without treatment.

**Treatment**

In 2013, the RLS Foundation’s Scientific and Medical Advisory Board published an updated consensus statement for the management of RLS in the *Mayo Clinic Proceedings*. Providers treating individuals with RLS should consult this statement. In 2016, the IRLSSG, EURLSSG and the RLS Foundation’s Scientific and Medical Advisory Board published new guidelines for first-line treatment of RLS including the prevention and treatment of dopaminergic augmentation.

The first step in treating a person diagnosed with RLS is to determine the frequency and severity of the RLS symptoms. One treatment algorithm assigns individuals to three categories reflecting increasing severity of the disorder. Use of the classification in Table 6 is recommended.

**Table 6. Classification of RLS**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Intermittent RLS</strong></td>
<td>Symptoms of RLS are troublesome enough when present to justify treatment, usually occurring on average less than twice a week.</td>
</tr>
<tr>
<td><strong>Chronic Persistent RLS</strong></td>
<td>Symptoms of RLS are frequent and troublesome enough to require daily treatment, usually occurring at least twice a week on average.</td>
</tr>
<tr>
<td><strong>Refractory RLS</strong></td>
<td>Symptoms of chronic persistent RLS are unresponsive to monotherapy with first-line agents.</td>
</tr>
</tbody>
</table>

Several additional reviews of RLS treatment are available including the IRLSSG’s evidence-based and clinical consensus best practice guidelines for the long-term management of RLS.

**Non-Pharmacologic Therapy**

For individuals with intermittent RLS, non-pharmacologic approaches should be tried before prescribing medications that may have unwanted side effects, especially in the geriatric population (Table 7). Individuals should follow a regular sleep schedule and good practices for healthy sleep (e.g., reserving bed for sleep and intimacy; avoiding stimulant substances near bedtime; ensuring the bedroom is dark, quiet, and cool).
### Intermittent RLS

- Follow regular sleep schedule and healthy sleeping habits, including a trial of abstinence from caffeine which can disrupt sleep.
- Check serum ferritin/iron panel.
- Engage in mild-to-moderate physical activity.
- Try hot or cold baths to reduce symptoms.
- Recommend, as appropriate for age, mental-alertness activities such as video games or crossword puzzles.
- Schedule sedentary activities in the morning when symptoms are least bothersome.
- Stop or avoid certain drugs that can aggravate RLS symptoms. These include many antidepressants, neuroleptic agents, dopamine-blocking antiemetics such as metoclopramide, and sedating antihistamines.40,41

### Chronic Persistent RLS

The non-pharmacologic approach for chronic persistent RLS is the same as for intermittent RLS.

**Pharmacologic**

- Immediate release carbidopa/levodopa (25mg/100mg) or sustained-release (25mg/100mg).
- Low-potency opioid analgesics such as codeine or tramadol.
- Sedative-hypnotics such as eszopiclone, temazepam, zaleplon, or zolpidem (use the lowest effective dose) can be considered, especially if there is concomitant poor sleep or insomnia.

### Refractory RLS

The non-pharmacologic approach for refractory RLS is the same as for intermittent RLS.

**Pharmacologic**

- Check individual’s iron status and replenish iron as indicated with serological follow-up to assess response to therapy.
- Consider other possible exacerbating factors and correct if possible.
- Consider combination therapy with a dopamine agonist, an alpha-2-delta ligand, and/or benzodiazepine.
- Consider these opioids as either monotherapy or as an adjunct therapy with other RLS medications:
  - codeine, hydrocodone, oxycodone (Immediate or extended-release agents)
  - morphine, oxymorphone, hydromorphone (Immediate or extended-release agents)
  - methadone, buprenorphine, fentanyl patch (long-acting agents)
  - tramadolan, pentazocine (atypical agents)

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Mild-to-moderate physical activity involving the limbs (e.g., stretching exercises just before bedtime), hot or cold baths or any age-appropriate engrossing mental alerting activity may be of value. Individuals with RLS should consider adjusting their schedules to better accommodate their RLS symptoms. Sedentary activities like watching a movie or taking a long airplane flight may be better suited to the morning, whereas activities that require walking, such as housework or exercise, may help relieve RLS symptoms when performed later in the day. When traveling long distances, alerting activities or engaging in feasible movement activities...
### Table 8. Pharmacologic therapy for RLS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
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<tr>
<td>Dopamine precursors</td>
<td>• carbidopa/levodopa (Sinemet)</td>
<td>Many individuals who take levodopa daily may develop augmentation.</td>
</tr>
<tr>
<td></td>
<td>• benserazide/levodopa (Madopar)</td>
<td>Therapeutic effect may be reduced if taken with high-protein food. Can</td>
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<tr>
<td></td>
<td></td>
<td>cause insomnia, sleepiness, and gastrointestinal problems.</td>
</tr>
<tr>
<td>Dopamine receptor agonists FDA approved for the treatment of RLS</td>
<td>• pramipexole (Mirapex)</td>
<td>Dopamine agonists can also cause nausea and hypotension. May cause augmentation,</td>
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<tr>
<td></td>
<td>• ropinirole (Requip)</td>
<td>but less likely to do so than levodopa. Associated with impulse control disorders.</td>
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<td></td>
<td>• rotigotine (Neupro)</td>
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<td></td>
<td>Levodopa can be used on a “one-time” basis or as circumstances may require such as extended travel by plane or car. Useful for individuals with intermittent RLS because dopamine receptor agonists take longer to have an effect. May also be used to help confirm RLS diagnosis.</td>
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<tr>
<td><strong>Alpha-2-delta ligands</strong></td>
<td>Alpha-2-delta ligands are alternative first-line agents for chronic persistent RLS. Alpha-2-delta ligands offer an effective alternative treatment when RLS is not effectively treated with dopaminergic agents.</td>
<td>Alpha-2-delta ligands can cause daytime sleepiness, gait unsteadiness, and cognitive impairment, particularly in the elderly, as well as weight gain and depression. Disadvantages can vary depending on the specific agent, but generally may include nausea, sedation, dizziness, and dermatologic conditions.</td>
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<tr>
<td>gabapentin (Neurontin)</td>
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<tr>
<td>gabapentin enacarbil (Horizant)</td>
<td>FDA approved for treatment of RLS</td>
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<tr>
<td>pregabalin (Lyrica)</td>
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<tr>
<td><strong>Opioids</strong></td>
<td>Opioids offer an effective alternative when RLS is not effectively treated with dopaminergic agents. They can be used on an intermittent or daily basis. They have a wide range of potencies, available in immediate or extended-release formulation.</td>
<td>Can cause constipation, urinary retention, sleepiness, or cognitive changes. Can exacerbate obstructive sleep apnea or induce central sleep apnea. Tolerance and dependence possible with higher doses of stronger agents, especially those with a shorter half-life.</td>
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<tr>
<td>morphine derivatives: morphine, hydromorphone, oxymorphone, oxycodone, hydrocodone, and codeine</td>
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<td>methadone</td>
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<td>buprenorphine</td>
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<td>fentanyl patch</td>
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<td>levorphanol</td>
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<tr>
<td>pentazocine (only kappa-opiate receptor agonist)</td>
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<tr>
<td>tramadol</td>
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<tr>
<td><strong>Sedative-hypnotics</strong></td>
<td>Sleep aids are most effective for improving sleep quality for individuals who experience RLS symptoms at night. They are usually used in combination with other agents.</td>
<td>Can cause daytime sleepiness, gait unsteadiness and cognitive impairment, especially in the elderly. Note: Do not use a benzodiazepine (temazepam, clonazepam) at the same time as an opiate medication.</td>
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<tr>
<td>Benzodiazepines (temazepam, triazolam, clonazepam)</td>
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<tr>
<td>Highly Selective Benzodiazepine Receptor Agonists (zolpidem, zaleplon, eszopiclone)</td>
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<tr>
<td>Orexin receptor antagonist (suvorexant)</td>
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may help alleviate symptoms. It is also helpful to examine other substances the person is taking that may exacerbate his or her RLS symptoms, including both over-the-counter and prescription medications. Any dopamine-blocking agent can aggravate RLS, and these include almost all the neuroleptics plus many anti-nausea agents. Many antidepressants may aggravate RLS symptoms. However, bupropion (Wellbutrin), a dopamine-active antidepressant, may prove to be the most preferred antidepressant for the patient with RLS. Among over-the-counter medications, centrally active (mostly sedating) antihistamines may be the greatest culprits. These are often found in over-the-counter medications to treat colds, allergies or promote sleep. Other substances that can provoke RLS symptoms directly or by way of interfering with sleep include alcohol, caffeine, decongestants that include sympathomimetic drugs (e.g. pseudoephedrine, phenylephrine), and melatonin.

Curative therapy may be available to treat the underlying disorder in secondary RLS, like iron deficiency or renal failure (see page 13, “Secondary RLS”). Resolving the underlying disorder may then eliminate RLS. Pharmacologic therapy varies with the individual’s form of RLS. The FDA has approved four medications for the treatment of RLS: three non-ergot dopamine agonists – ropinirole (Requip), pramipexole (Mirapex), and the rotigotine patch (Neupro) – and gabapentin enacarbil (Horizant), an alpha-2-delta ligand. However, this addresses only a subset of individuals with RLS. Other medications without FDA approval for RLS are often used off-label to treat different clinical situations or to manage individuals who cannot tolerate first-line therapy dopamine agonists or alpha-2-delta ligands.

**Pharmacologic Therapy**

Pharmacologic therapy of RLS is designed to relieve the individual’s sensorimotor symptoms and sleep disturbances. Such therapy is symptomatic and does not cure RLS, but merely suppresses the disorder’s unwanted manifestations. In the case of augmentation, the treatment (paradoxical reaction of a dopaminergic agent) may actually make RLS worse over time (see page 9, “Refractory RLS”).

**Intermittent RLS**

Therapy of intermittent RLS involves a review of appropriate non-pharmacologic strategies with the individual. The use of a wide variety of pharmacologic agents (Table 8) are directed at specific problems. The drug carbidopa/levodopa (Sinemet) is helpful for intermittent RLS, but often causes augmentation when used regularly so that it is not recommended for daily treatment of RLS. Carbidopa/levodopa or opioid may be useful when symptoms are unpredictable (e.g., an airplane trip, a long car ride, a theatrical event, etc.) because they do not require dose titration to be effective. When the main problem is sleep disruption (either difficulty initiating or maintaining sleep), a sedative hypnotic or opioid may be useful.

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**Table 9. Rebound, augmentation, and impulse control disorders**

<table>
<thead>
<tr>
<th><strong>Rebound</strong></th>
<th>is the return of RLS symptoms late in the night or in the morning, generally considered the result of dropping drug levels. This occurs more commonly with short acting drugs like Mirapex or Requip.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Augmentation</strong></td>
<td>is an increase in RLS severity after initial response of RLS symptoms to medicine (can last for years) that: 1. Occurs on at least 5 of 7 days 2. Is not accounted for by other factors (e.g., new medication, blood loss, activity change) AND occurs with either: • “Paradoxical response” with increased symptoms when dose is increased and decreased symptoms when drug is decreased OR • Advance in time of symptoms either by 4 hours, or 2 hours with at least two of the following: a. shorter latency to symptom onset at rest b. spread to previously unaffected body parts such as the trunk, arms or face c. increased intensity of symptoms or PLM d. shorter duration of relief from treatment</td>
</tr>
<tr>
<td><strong>Clinically significant augmentation</strong></td>
<td>is present when there is impact on the patient’s life indicated by a necessary medication change, change in activities undertaken, or decreased quality of life.</td>
</tr>
<tr>
<td><strong>Impulse control disorders</strong></td>
<td>occur in 6 to 17 percent of individuals with RLS who take dopamine agonists as first-line therapy. Behaviors include pathologic gambling, impulsive shopping, and hypersexual behavior. On average, symptoms typically commence nine months after initiation of dopamine agonist therapy.</td>
</tr>
</tbody>
</table>

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Impact on the patient’s life indicated by a necessary medication change, change in activities undertaken, or decreased quality of life.
Chronic Persistent RLS

Treatment of chronic persistent RLS should begin with an examination of non-pharmacologic interventions that may improve quality of life and reduce symptoms. First-line medication therapy for chronic persistent RLS includes a non-ergot dopamine agonist (pramipexole, ropinirole, or the rotigotine transdermal patch) or an alpha-2-delta ligand (gabapentin, gabapentin enacarbil or pregabalin). Because alpha-2-delta ligands can cause depression and weight gain, one of the dopamine agonists is the more appropriate choice in the presence of mood disorder or obesity. Alpha-2-delta ligands can alleviate RLS symptoms that are characterized as painful and may be helpful when the co-morbid conditions of anxiety or insomnia are present. For RLS symptoms that are present throughout much of the day and night, a long-acting agent such as the rotigotine transdermal patch or gabapentin enacarbil should be considered.

Non-ergot agonists are favored over ergot-derived agonists because they seem less likely to cause a rare but potentially serious complication of fibrosis (pleuro-pulmonary fibrosis or fibrotic cardiac valvulopathy). In fact, pergolide, an ergot agonist that was quite successful in treating RLS, was withdrawn from the US and Canadian markets. In the future, other non-ergot agents or formulations may also be approved or available off-label.

It is important to note that the use of dopamine agonists is often complicated by augmentation, a worsening of RLS (see page 11, Augmentation) that often occurs in the setting treatment of RLS with a dopaminergic medication. A recent US community-based study estimated that 76 percent of all patients treated with dopaminergic agents required either a dose increase and/or showed indications for partial or full augmentation, with a yearly incidence rate of approximately 8 percent. Because of this, many healthcare providers are beginning to use an alpha-2-delta ligand as first-line treatment.

Not all agree with this practice; however, if a dopamine agonist is to be used as initial therapy it is extremely important to use the lowest effective dose and not to exceed the maximum recommended dose of drug for RLS (pramipexole 0.5–0.75 mg; ropinirole 4 mg; rotigotine 3 mg). It may be helpful to keep doses as low as 0.25 mg pramipexole or 1.0 mg ropinirole to reduce the likelihood of augmentation. Further, the prescriber should avoid the temptation to use higher doses of dopamine agonists that may be used in individuals with Parkinson’s disease, where doses of ropinirole can exceed 20 mg. The use of supratherapeutic doses of dopamine agonists greatly increases the risk of developing another serious side effect of dopaminergic medication usage, impulse control disorders (Table 9).

Refractory RLS

There is little medical literature on how to address refractory RLS. The current recommendations are based on the clinical opinion of experts who have had extensive experience in managing the more difficult cases of RLS.

Several strategies may be useful in managing refractory RLS:

1. The individual’s iron stores should be rechecked and, if serum ferritin is less than 75 mcg/L, oral or intravenous iron therapy should be initiated.
2. As with both intermittent and chronic persistent RLS, other exacerbating factors should be identified and addressed.
3. Consider using a combination of drugs. This may allow reducing the dosage of the primary agent to avoid adverse effects while adding a different drug class to permit expanded coverage. Typical combinations have seen dopamine agonists paired with alpha-2-delta ligands, opioids, or sedative-hypnotics. Opioids may best address waking symptoms, while alpha-2-delta ligands and sedative-hypnotics may be particularly useful for decreasing sleep problems.
4. Consider using recommended doses of opioids such as oxycodone, hydrocodone, or methadone. Individuals who have failed numerous medication regimens may be managed with the use of opioid medications.

Medications

Dopaminergic Agents

Although dopaminergic agents have been recognized as the mainstay of RLS pharmacologic therapy for the past 20+ years, their use has slightly fallen out of favor as augmentation caused by these medicines is becoming increasingly prevalent and recognized.

The dopamine precursor levodopa is converted to dopamine in the brain. Levodopa is formulated together with a decarboxylase inhibitor to prevent peripheral catabolism and reduce adverse effects due to peripheral actions (nausea, hypotension). Typical doses are in the range of 25 mg/100 mg to 50 mg/200 mg (carbidopa/levodopa) usually taken one hour before symptom onset. Effectiveness on the first night of use at low doses supports the feasibility of intermittent or as-needed use of levodopa, as well as its use in a therapeutic trial for individuals in whom the diagnosis of RLS is in doubt. It has typical dopaminergic side effects, which include nausea, vomiting, headache, somnolence, and dizziness. It can be quite effective acutely in treating RLS, but because it so readily causes augmentation, it is best used only for intermittent treatment. A formulation with benserazide has been approved for treating RLS in several European countries.

Dopamine agonists have the usual dopaminergic side effects and can cause peripheral edema. They are associated in RLS with impulse control disorders (e.g. pathologic gambling, excessive shopping, hypersexuality), with a frequency of 6 to 17 percent in
prospective studies. This complication develops a mean of 9 months after treatment onset, so it is essential to repeatedly warn individuals and inquire about symptoms at each subsequent visit. The consequences of unrecognized impulse control disorders can be devastating, including substantial financial loss and the threat of criminal prosecutions. However, complete resolution of the pathologic tendencies is the general rule with discontinuation or dose decrease of the causative agent. There is evidence that somnolence, including sleep attacks, occurs in individuals taking dopamine agonists to treat RLS. This may be dose related so care should be taken to use the lowest effective dose. A transdermal formulation of rotigotine has been shown to be

Table 10. Dosing schedule for RLS

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbidopa/levodopa (Sinemet)</td>
<td>Typical initial doses are a half or whole tablet of 25 mg/100 mg (carbidopa/levodopa) usually taken one hour before symptom onset.</td>
<td>It is not recommended to exceed a dose of 50 mg/200 mg (carbidopa/levodopa) in immediate or sustained-release formulations due to the very high risk of augmentation.</td>
</tr>
<tr>
<td>pramipexole (Mirapex)</td>
<td>The initial dose is typically 0.125 mg and is titrated upward to avoid side effects such as nausea and orthostatic hypotension.</td>
<td>The mean effective dose from multiple studies is approximately 0.375 mg. Individuals typically habituate to side effects in a matter of 7 to 10 days. Maximum recommended dose approved by the FDA for treating RLS is 0.5 mg.</td>
</tr>
<tr>
<td>ropinirole (Requip)</td>
<td>The initial dose is typically 0.25 mg and is titrated upward every 2 to 3 days in order to avoid side effects such as nausea and orthostatic hypotension.</td>
<td>The average individual responds to a total dose in the 1.0-2.5 mg/day range. Individuals with RLS typically habituate to side effects in a matter of 7 to 10 days. Maximum recommended dose approved by the FDA for treating RLS is 4 mg/day.</td>
</tr>
<tr>
<td>rotigotine patch (Neupro)</td>
<td>The initial dose is a 1 mg patch worn over a 24-hour period. Increase as needed by 1 mg/24 hours at weekly intervals.</td>
<td>Maximum recommended dose approved by the FDA for treating RLS is 3 mg/24 hours. The prescribed dose may be achieved using single or multiple patches.</td>
</tr>
<tr>
<td>Alpha-2-delta ligands</td>
<td>• gabapentin (Neurontin) 100–300 mg • gabapentin enacarbil (Horizant) 300–600 mg • pregabalin (Lyrica) 50–75 mg</td>
<td>• gabapentin 3,600 mg/day • gabapentin enacarbil FDA approved dose is 600 mg at 5 pm with food. 1,200–1,800 mg at 5 pm may be helpful, but is off label use. • pregabalin 450 mg/day</td>
</tr>
<tr>
<td>Opioids</td>
<td>• codeine 15–30 mg as compound • oxycodone 5–10 mg • oxycodone XR 10 mg • tramadol 50–100 mg • hydrocodone 5–10 mg • methadone 5–10 mg</td>
<td>• codeine 120 mg/day • oxycodone 15–20 mg/day • oxycodone XR 20–40 mg/day • tramadol 300–400 mg/day • hydrocodone 20–30 mg/day • methadone 20–30 mg/day</td>
</tr>
<tr>
<td>Sedative-hypnotics</td>
<td>• eszopiclone 1 mg • temazepam 7.5–15 mg • zaleplon 5 mg • zolpidem 5 mg</td>
<td>• eszopiclone 3 mg • temazepam 30 mg/day • zaleplon 20 mg • zolpidem 10 mg in men; 5 mg in women</td>
</tr>
</tbody>
</table>
effective in large-scale trials. This longer-acting dopamine agonist has the benefit of being less likely than other dopamine agonists to cause augmentation. In Europe, researchers have extensively studied the use of cabergoline for RLS, but it is difficult to obtain affordable dosages in the U.S. where the drug is only approved to treat pituitary adenomas. In Canada, it can also be financially challenging to obtain appropriate dosages of this drug because it is generally not covered under provincial healthcare plans. In addition, it is an ergot-based agonist with a significant tendency to cause fibrotic conditions, including cardiac valvulopathies. Lisuride has also been tested in Europe, and it has been suggested that there may be less fibrosis than with other ergot compounds due to its distinctive receptor binding. The typical phenomena that has limited the use of dopamine agonists in Parkinson’s disease, such as motor fluctuations, dyskinesias, hallucinations, and psychosis, have been rare problems for individuals with RLS, perhaps because of the different biology and lower doses used. For RLS, augmentation is the side effect that limits the long-term use of the dopaminergic medications. Augmentation occurs in the setting of chronic dopaminergic medication usage, usually in doses that have escalated over time.

**Augmentation**

Augmentation currently receives the greatest attention in cases of refractory RLS. Augmentation is an iatrogenic worsening of RLS with one or more of the following features: an advance of the typical time of day when symptoms begin 2 or more hours earlier than before the start of treatment; a spread of restlessness from the legs to the arms or trunk; a shorter interval before symptoms start after adopting a quiescent position (Table 9).

Augmentation requires that the individual demonstrated at least some initial response to medication, the exclusion of other possible causes for a worsening of symptoms, and a consistent change in symptoms.

RLS symptoms can vary from day to day and wax and wane over longer time periods, so one day or just a couple of days of worsened symptoms are insufficient to diagnose augmentation. Because of the increasing prevalence of augmentation the RLS Foundation’s Scientific and Medical Advisory Board published a guideline outlining the identification and treatment of augmentation. The presence of one or more of the following factors are known to increase the likelihood of augmentation: (1) more frequent RLS symptom pretreatment; (2) greater discomfort with RLS symptoms before treatment; (3) comorbid asthma; (4) older age; (5) longer treatment duration; (6) lower serum ferritin levels; and (7) greater baseline severity of RLS.

These four screening questions were recommended to identify augmentation:

1. Do RLS symptoms appear earlier than when the drug was first started?
2. Are higher doses of the drug now needed, or do you need to take the medicine earlier, to control the RLS symptoms compared to the original effective dose?
3. Has the intensity of symptoms worsened since starting the medication?
4. Have symptoms spread to other parts of the body (e.g., arms) since starting the medication?

Augmentation is considered mild if all of the following are present: symptoms manifest predominantly as a temporal shift of symptoms to earlier in the day compared to before starting treatment; dopaminergic monotherapy is at a total daily dose at or below maximum recommended levels; symptoms cause only mild distress; and there has been no prior increase in total dose above that which was previously therapeutically effective. Augmentation is considered severe if it does not fulfill the criteria for mild augmentation (eg, the total agonist dose exceeds recommended levels or the symptoms cause more than mild distress), or does not respond to treatment of mild augmentation (Table 11).

**Treating Augmentation**

Table 11 shows a treatment algorithm for augmentation. Initially, it is important to identify and eliminate or treat exacerbating factors; these could include poor sleep hygiene, ingestion of drugs/foods that worsen RLS symptoms, or low serum ferritin. If the iron stores are low then iron therapy (oral or intravenous) should be used.

For mild augmentation, the dopamine agonist medication could be continued and the total dose maintained but given in divided doses, or the medication could be given earlier to precede the onset of RLS symptoms. Alternatively, the dose of dopamine agonist could be increased (but not to exceed the recommended maximum for RLS). Often if given once in the evening and once at bedtime, the earlier dose may be increased. If these dose adjustments fail, then a switch to another medication is recommended. Possible alternative medications are any of the alpha-2-delta ligand medications or a longer acting dopamine agonist such as rotigotine. Failure of a switch to one of these medications warrants classification of ‘severe augmentation’ and beginning one of the severe augmentation treatment strategies.

For severe augmentation, a cross titration with an alpha-2-delta ligand or rotigotine while the shorter acting dopamine agonist is tapered off, is a strategy that eventually improves RLS control. Also a ten-day washout period is another strategy, in which a dopamine agonist is tapered off and no new medication is initiated until the dopamine agonist is stopped. At the end of the washout period, a new drug may be introduced. Advantages of the ten-day washout are that it enables evaluation of the degree of
**Table 11. Algorithm for Augmentation**

Eliminate exacerbating factors (serum ferritin < 50-75 µg/L, lifestyle changes, exacerbating drugs)

**Mild augmentation (all of the below)**
1. Temporal shift
2. Dopaminergic dose is ≤ maximum recommended dose
3. Symptoms cause mild distress
4. There has been no prior increased dose above what was previously therapeutically effective

**Keep the same dopamine agonist** OR **Complete switch to one of the options below**

One of the below three options:
1. Split with same dose; 2. Advance the dose earlier.
   If options 1 and 2 fail 3. Consider increasing the dose but keeping it at/ below approved daily dose

If this strategy fails consider a complete switch of medication

**Severe augmentation**
1. Not mild. OR 2. Does not respond to treatment for mild augmentation

The objective is to reduce, & if possible eliminate the short-acting dopamine agonist and to begin treatment with rotigotine or a long-acting dopamine agonist or an alpha-2-delta ligand or in severe cases a long-acting opiate. Three strategies are available for doing this:

**Cross titration**
Add an alpha-2-delta ligand and then gradually reduce the dose of the dopamine agonist with the objective of eliminating it altogether, understanding that this may not be possible in all cases

**Switch**
Switch patient from a short-acting dopamine agonist to rotigotine or a long-acting dopamine agonist if this is not already the case

**OR**

**10-day washout**
Evaluate if any drug treatment is needed. If symptoms continue introduce an alpha-2-delta ligand or an opioid

If these strategies fail or if the patient has severe, round-the-clock symptoms, then treatment with low doses of an opioid (long-acting oxycodone or methadone) should be considered.

If serum ferritin < 50–75 µg/L then treatment with intravenous iron, according to availability, should be strongly considered.

The treatment guidelines outlined in Table 11 suggesting a ferritin <50-75 mcg/L, did not have available more recently published studies. Two recent randomized, controlled trials of IV iron therapy in non-anemic RLS patients with a ferritin level less than 300 mcg/L demonstrated significant treatment benefits.

RLS symptoms on no medication. The disadvantage is that this often leads to transitory extremely severe RLS symptoms and profound insomnia during the washout period that may last four to fourteen days. In patients with continued severe RLS symptoms, low dose of opioid medication (oxycodone prolonged release 5–40 mg or methadone 2.5–30 mg) may be helpful. Special consideration should be given to risk of addiction (family or personal history of drug abuse, psychiatric comorbidities) and comorbid medical issues (e.g. pre-existing severe constipation, sleep apnea, prolonged QT).
Alpha-2-Delta Ligands

The most experience in RLS has been with gabapentin, which has shown promise in the treatment of RLS and associated sleep disturbance.76 Gabapentin is generally well tolerated but can cause sedation, dizziness, and unsteadiness, especially in older individuals. It has been tested in head-to-head trials against dopaminergics with generally comparable results.77,78 Gabapentin has less drug-drug interactions due to its renal route of excretion. It may be particularly well suited for individuals with comorbid RLS and peripheral neuropathy, and it is often used as an adjunctive agent in RLS with persistent sleep disturbance due to its mild sedative properties. Pregabalin, a related compound, has been shown in controlled trials to be effective in managing RLS.13 A gabapentin pro-drug, gabapentin enacarb, has also been shown to be effective and was FDA approved for the treatment of moderate to severe RLS in 2011. It is administered as a single daily dose of 300-600 mg at 5:00 pm with food. Doses can be increased to 1,200 or 1,800 mg at 5:00 pm, but practitioners should keep in mind that use of gabapentin enacarb at doses over 600 mg for RLS are off-label. Side effects for the alpha-2-delta ligand class include drowsiness, dizziness, unsteadiness, weight gain, and depression. Pregabalin has the added advantage over dopamine agonists of improving sleep.

Opioids

Opioid medications have been known to bring relief from RLS since first described by Willis in the 17th century.72 Although opioids are frequently prescribed by RLS experts, there have been relatively few published reports of their use. There is one successful double-blind study of oxycodone,79 one double-blind study of oxycodone-naloxone,131 and three long-term clinical series indicating the usefulness of opioids.47,74,113 The selection of any individual opioid is largely based on physician preference. For individuals with very severe, nearly continuous RLS symptoms, oral methadone has been found to be useful because of its long half-life.47 No cases of augmentation have been described with opioid use in RLS except for a small number reported for tramadol.79 Side effects include nausea, gait unsteadiness, sedation, dizziness, and constipation. Use of opioids may induce or exacerbate obstructive or central sleep apnea. There are also concerns about abuse potential, addiction, and practical problems (e.g., transfer to non-patients when medications are not secure) arising from the use of “controlled” drugs, and prescribers need to be sensitive to such issues. As a result, many physicians and patients are not comfortable using narcotic medications to treat a long-term condition. Nevertheless, opioids often provide significant relief for RLS when other treatments have failed and may represent the optimal treatment for some individuals.

Sedative-Hypnotics

Benzodiazepines (particularly clonazepam) have been used commonly to treat RLS; however, they should be used as more of an add-on medication when RLS symptoms are treated with a first-line RLS agent, but poor sleep persists. In more recent years, because of the efficacy of the dopaminergic agents and alpha-2-delta ligands, the benzodiazepines are less used and have appropriately become second-line agents in the treatment of RLS. Poor sleep often accompanies RLS. Benzodiazepine receptor agonists, which are commonly thought of as more traditional “sleeping pills,” can be helpful when sleep initiation and/or maintenance is a problem. The benzodiazepine receptor agonists should not be used to treat RLS symptoms, but rather insomnia that persists despite treatment of RLS.

As there is some misuse potential, as with opioids, careful screening for past drug or alcohol misuse, abuse, or dependency is important, and close monitoring is necessary.

Secondary RLS: RLS Associated with Other Conditions

End-Stage Renal Disease (ESRD)

It has been recognized for over 45 years that, in comparison to the general population, RLS is more common in individuals with end-stage renal disease (ESRD) both before and after the institution of dialysis. Recent prevalence studies indicate that the rates of RLS among this patient group range from 6 to 83 percent, varying with racial groups and with modes of management. Both RLS and a PLM index greater than 20 are significant independent predictors of mortality in this population.82,83 Quality of life is also adversely affected.84,85 The causes of the high prevalence of RLS in ESRD remain to be fully described. Anemia has been linked to RLS, and normalization of hematocrit with recombinant erythropoietin has resulted in a significant reduction in PLM.85 Most general RLS medications work in uremia, although doses and their timing may need to be adjusted to compensate for kidney failure. Conversely, higher doses may be needed to adequately control symptoms.102 Successful transplantation, but not dialysis, improves and sometimes cures RLS in uremia.

Pregnancy

Pregnancy may be the first time a woman experiences RLS symptoms or her pre-existing RLS may be exacerbated during pregnancy. RLS is common during pregnancy – it affects approximately one in five pregnant women in Western countries.55 RLS is the third most common cause of insomnia during pregnancy62 and emerging data indicate increased risk of preeclampsia, caesarian delivery, and depressed mood with RLS.56-58 The prevalence and severity of RLS progressively increase over the course of pregnancy, peaking in the third trimester, but then drop precipitously around delivery and RLS resolves completely in about 70 percent of cases.63-65 However, transient RLS during pregnancy confers a four-fold increased risk of later
developing RLS, independent of pregnancy.79 Treatment of RLS in pregnant women is hampered by limited information about the efficacy and safety of treatments during pregnancy.208 Recent consensus guidelines recommend nonpharmacologic approaches for most women, which include education, reassurance, moderate exercise, and avoidance of exacerbating factors. In addition, iron supplementation is suggested, if iron status is not optimal.55,80 For more information, please see the separate brochure entitled Pregnancy and RLS: Vital considerations in treating a pregnant patient who has restless legs syndrome (RLS), available for member download at www.rls.org.

**Iron Deficiency**

Serum levels of ferritin, the primary storage unit for iron, have been found to correlate inversely with RLS severity.35,36 The lower the iron level and the more acute the onset of symptoms, the more likely it is that improvement can be expected in RLS symptoms with iron supplements. Raising ferritin levels to above 75–100 mcg/L may be helpful. Iron treatment can be instituted with ferrous sulfate, 325 mg once a day with 500 mg of vitamin C or a small glass of acidic orange juice (to acidify the stomach and promote absorption) or comparable doses of elemental iron. “Organic” iron preparations, where iron is attached to an amino acid rather than a salt, are better tolerated but more expensive. Intravenous iron dextran improved RLS in open label trials88,89 but an iron sucrose infusion failed to do so in one double-blind trial.90 Results from infusion studies are mixed, and it may depend on the specific type of iron infused.132 Low molecular weight iron dextran (INFeD) is preferred over the older high molecular weight iron as it is much safer. There have been four randomized, double-blind, placebo-controlled studies of IV iron in RLS patients who were not anemic. The base inclusion criteria for iron status was a ferritin < 300 mcg/L and percent transferrin saturation < 45 percent. Two studies used iron sucrose and two studies used ferric carboxymaltose (FCM). All studies gave a final dose of 1000 mg. One sucrose study, had a final outcome measure at only two weeks. It is now apparent from clinical trials that the effects of IV iron require about 6 weeks to have maximal effect. So not surprisingly the 2-week trial with iron sucrose did not find a benefit. The second study with iron sucrose had significant benefit compared to placebo at 7 weeks but not at 11 weeks, which was the defined endpoint for the study. Patients, however, were followed for a full year without breaking the blind. At 1 year nearly 85 percent of the treatment groups, versus 37 percent of the placebo groups, reported continued benefits. Both of the FCM studies found treatment to be significantly better than placebo at their respective primary endpoints. Also both studies showed about 30–35 percent of those treated continued to have sustained benefits 26 or more weeks after the initial treatment.

There are a number of intravenous iron preparations available; iron infusion therapy with low molecular weight iron dextran (INFeD) or ferric carboxymaltose (Injectafar) is recommended in treating RLS symptoms. Specific predictors on who benefits from intravenous iron are lacking. In view of the uncertainties, this therapy is usually reserved for individuals with a diagnosis of definite iron insufficiency who have malabsorption states preventing oral iron absorption or complete intolerance to oral iron preparations, or individuals refractory to other treatments. With the institution of oral iron supplementation, serum ferritin levels and percent transferrin saturation (% sat) should be checked at intervals not longer than every three months. Supplemental iron should not be continued if % sat >50 percent given the risks of hemochromatosis.91 Low ferritin or anemia may also be a sign of bleeding and may indicate the need for a workup. RLS has been the presenting symptom of colon cancer, which can cause internal bleeding.92

<table>
<thead>
<tr>
<th>Table 12. Special considerations for diagnosis of RLS in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The child must describe the RLS symptoms in his/her own words.</td>
</tr>
<tr>
<td>• The diagnostician should be aware of the typical words children and adolescents use to describe RLS.</td>
</tr>
<tr>
<td>• Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age.</td>
</tr>
<tr>
<td>• It is not known if the adult specifiers for clinical course apply to pediatric RLS.</td>
</tr>
<tr>
<td>• As in adults, a significant impact on sleep, mood, cognition, and function is found. However, impairment is manifested more often in behavioral and educational domains.</td>
</tr>
<tr>
<td>• Simplified and updated research criteria for probable and possible pediatric RLS are available.</td>
</tr>
<tr>
<td>• Periodic limb movement disorder (PLMD) may precede the diagnosis of RLS in some cases.</td>
</tr>
</tbody>
</table>

Children and RLS

RLS in Children

Recent literature reveals that RLS occurs frequently in children, exceeding the prevalence of both pediatric epilepsy and diabetes. Population-based studies in the United States, United Kingdom, Turkey, and China have found a prevalence of 2 to 4 percent, with 0.5 to 1 percent of the total pediatric population having moderate to severe RLS.81,86,87,9 The impact can be substantial, particularly on sleep, cognitive function, and affect.81,90,100,103 Young children present a diagnostic challenge since many symptoms of RLS are subjective and difficult to explain, even for adults. The first consensus, pediatric-specific diagnostic criteria were developed at a workshop at the National Institutes of Health in May 2002 and subsequently updated in 2013.104,105 In addition, probable and possible RLS categories were developed to promote research in this area. For more information, please see the separate brochure entitled Children and RLS: Restless Legs Syndrome and Periodic Limb Movement Disorder in Children and Adolescents, available for download at www.rls.org.

Diagnosis of RLS in Children

As in adults, the symptoms of RLS in children may include leg discomfort, sleep onset problems, and sleep maintenance problems.108-110 In some children, RLS discomfort may be misdiagnosed as “growing pains.”111,112 The pediatric diagnostic criteria were simplified and integrated with the newly revised adult RLS criteria in 2013.105 However, diagnosis in children requires both an understanding of the adult features of RLS and how the criteria apply to children. Table 12 highlights the special considerations for diagnosis of pediatric RLS. Most important is awareness of how children describe their symptoms: “urge to move” is almost never used and, in younger children, not typically understood. Rather, “have to move,” “need to move,” and “got to kick” are common descriptors children use.109

Having the child draw a picture of the symptoms can be helpful.109 It is important to differentiate pediatric RLS from mimics such as positional discomfort, sore muscles, arthralgias, and dermatitis.

Features seen in children that support an RLS diagnosis include periodic limb movements in sleep (PLMS), a family history of RLS among first-degree relatives, and a family history of PLMS > 5/hour.105 In children, periodic limb movement disorder (PLMD) can be a precursor to development of RLS.113 PLMD is diagnosed by polysomnography and/or accelerometry. Additional details about RLS and PLMD diagnosis in children can be found in recent publications.105,114

RLS and Behavioral Problems in Children

Research suggests that cognitive, behavioral, and affective difficulties, especially attention problems (attention deficit/hyperactivity disorder or ADHD) and anxiety may be more common in children with RLS.81,113,115,116 Further investigation is needed to understand the association of these disorders with RLS and PLMS. A possible biologic basis may lie in iron deficiency which has been associated with both RLS and ADHD.117,118

Treatment of RLS in Children

Although there is extensive evidence-based literature for the treatment of RLS in adults, there are limited treatment trials for RLS or PLMD in the pediatric population. Most evidence is gleaned from case reports, case series, extrapolation of adult data, and expert clinical opinion. Pediatric literature has indicated that children may benefit from a strict and consistent sleep schedule, restriction of caffeine, iron supplementation, and medications.114,117,120 However, recent emphasis has been on iron supplementation to attain optimal iron status, as measured by ferritin in the 50–100 mcg/L range.103,114,121-124 A current review suggests a progressive approach, which includes nonpharmacologic interventions, iron supplementation, and medication based on severity of symptoms.114 First-line medications suggested are gabapentin, clonazepam, and clonidine.

References


