



DEPARTMENT OF  
NEUROLOGY

## Parkinson's Disease Center and Movement Disorders Clinic

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### Restless Legs Syndrome

#### Diagnosis

With the emergence of new approved treatments and increased public awareness, restless legs syndrome is now recognized to be one of the most common movement disorders. The diagnosis of RLS is entirely based on the symptoms that the patient reports. In 2012 an International Restless Legs Syndrome Study Group committee defined RLS as:

- A desire to move the limbs, often associated with unpleasant sensations
- Worsening of symptoms at physical and mental rest
- Complete or partial relief with movement
- Worsening of symptoms in the evening or night. Some patients, however, may lose the diurnal pattern so that their RLS may not necessarily worsen at night.
- The symptoms are not accounted for by another medical or behavioral condition

The sensations that people feel are always unpleasant but not necessarily painful. The most common descriptions used include such words as "need to move," "crawling," "tingling," "restless," "cramping," "creeping," "pulling," "painful," "electric," "tension," "discomfort" and "itching." These sensations are usually deep in the limbs and can be improved by rubbing, hot/cold water, and by any movement. Patients often get up to walk around in an attempt to relieve the irresistible restlessness. Despite the name, restless legs syndrome, these sensations may also be felt in the arms, although the legs are almost always more severely affected; the face and torso are rarely, if ever, involved. Since the sensations are worse at night, patients often have great difficulty falling asleep. This sleep deprivation can lead to a variety of other problems including memory

problems, depression, and even contribute to other medical problems such as hypertension.

Another feature that many patients with RLS have is called periodic limb movements of sleep (PLMS). These are kick-like movements of the legs while patients are asleep. They can also occur when patients are drowsy but not yet asleep. This is often more of a problem for the bed partner, who may get kicked, than the patient, who is often unaware of these sleep-related movements. Several surveys have now shown that RLS affects up to 7 percent of all people; women are more often affected than men. In one study the prevalence among people over the age of 50 was found to be 10.6 percent (14.2 percent in women, 6.6 percent in men). The chance of having RLS increases with age. RLS patients often do not see a physician until mid to later life but many actually report subtle symptoms dating from much earlier in their life. These symptoms typically worsen over time. The onset of mild symptoms during childhood or even infancy is not rare. Children, however, often do not report all the classical symptoms, and may just have irritability and difficulty concentrating. Some physicians feel that attention deficit hyperactivity disorder may actually be a form of RLS in certain cases, but this relationship has not yet been clarified. RLS appears in all ethnic backgrounds and nationalities, although people from European descent (Caucasian) seem most likely to have RLS.

There are no diagnostic tests available for RLS and the diagnosis of RLS remains a clinical one. There are, however, tests that can identify some of the diseases that can increase the risk of RLS, so-called "secondary RLS" (see below). Iron deficiency should be excluded and tests for peripheral neuropathy, such as an electrical test called "nerve conduction study" (NCS) and "electromyography" (EMG), may be warranted. Patients occasionally have sleep studies (polysomnograms) to document the leg kicking (PLMS).

### Cause

The exact cause of RLS is not known, but is believed to be secondary to iron deficit in the brain. The diagnosis of RLS is divided into a primary type and a secondary or symptomatic type. Patients with primary RLS have no other medical condition that causes their symptoms. In many cases of primary RLS there is a family history of similar symptoms in blood relatives. Therefore, this RLS is usually "genetic." Often patients do not know that other family members suffer from the same condition because the relatives usually do not share the information about their RLS symptoms with their relatives or even their physicians and, hence, have never been diagnosed with RLS. It is very important to identify other family members that may have RLS because an identification of large families with RLS may help researchers find gene or genes that cause RLS. Once this is accomplished, it will greatly improve our understanding of the condition and may lead to DNA diagnostic tests. Such tests could then be used to confirm the diagnosis and to identify individuals at risk for developing this condition. Most researchers feel that RLS is inherited in an autosomal dominant pattern, which means that if someone has primary (genetic) RLS, then each of their children has a 50 percent chance of inheriting the gene and possibly developing the symptoms. Current research has identified at least six genes that may be involved in RLS and more RLS-related genetic abnormalities are expected to be identified in the near future. Based on some animal models developed by scientists at Baylor College of Medicine (BCM), the lower part of the brain (brainstem) has been implicated in the pathophysiology of RLS.

Secondary RLS means that another medical condition is the cause, or at least is associated with RLS symptoms. Several common conditions including neuropathy, kidney failure, iron deficiency, essential tremor, pregnancy, and certain drugs can cause RLS symptoms. "Neuropathy" refers nonspecifically to any damage to a nerve or nerves (damage to the nerves in the legs occasionally leads to RLS). There are many specific causes of neuropathy, some of which are treatable, but most of which are not. Kidney or renal failure (uremia) is usually diagnosed easily with blood tests. Up to 1/3 of all patients with kidney failure have RLS. Iron deficiency is another potential cause and is usually measured by a blood test for

serum iron, ferritin as well as other blood tests. Iron-deficiency anemia may not be present. Up to 1/3 of all women experience RLS during the last trimester of pregnancy. Symptoms, however, improve shortly after delivery. Several other conditions may also be associated with RLS.

## Treatment

No two patients respond identically to treatments for RLS. All treatments are felt to provide only symptom relief, rather than a permanent cure for RLS. Therefore, treatment should only be started when the benefits are felt to justify any potential side effects and costs. RLS is a chronic condition and, therefore, treatment decisions should take into account potential long-term issues and be individualized to the particular needs of the patient. Both dosing and medication changes are often required to maximize benefit and minimize the risk of tolerance and side effects over time.

It is clear that intense physical and even mental activity can forestall RLS symptoms. The problem is of course that symptoms are worse when people are trying to fall asleep, which is not a convenient time to exercise. There are certain situations, such as a plane flight, where intense concentration (i.e., a challenging video game) may improve symptoms.

No natural or over the counter (OTC) medications consistently improve RLS. OTC sleeping medicines such as Benadryl (an antihistamine) and melatonin may actually worsen symptoms. Other substances that may worsen RLS include antidepressants (especially mirtazapine), alcohol, caffeine and nicotine which are therefore best avoided. Some patients report that calcium and magnesium help them, but when these were examined scientifically they did not show any benefit. OTC iron supplements may help some people, however iron pills only mildly increase iron in the body (although absorption can be enhanced by co-administration of vitamin C). Less than 1 percent of the pill is actually absorbed from the stomach. Because of potential side effects patients should always check with their physicians before taking any OTC medications.

By far, the most consistently effective treatments for RLS are prescription medications. No medication has been specifically developed for RLS, but fortunately medications developed for other condition often help RLS symptoms.

Dopaminergic medications, which replace or imitate a brain chemical called dopamine, were developed to treat Parkinson's disease (PD). It should be re-emphasized that RLS does not lead to PD, or any other neurological conditions, despite the fact that the same medications improve both PD and RLS. The first anti-PD drug found to help RLS was carbidopa/levodopa (Sinemet). While most RLS patients initially improve with levodopa, this improvement usually lessens over time. Sinemet is occasionally used to treat severe RLS in pregnant or breastfeeding women who have failed non-pharmacological measures and trigger avoidance. A series of other dopamine drugs called agonists (dopamine mimickers) have since been shown to markedly improve RLS symptoms, often more than Sinemet. These include pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro); these dopamine agonists are all approved for use by the Food and Drug Administration. No one drug is consistently better than the others. Side effects of these dopamine drugs are generally mild but may include nausea, lightheadedness associated with low blood pressure, sleepiness (often welcomed), and nasal congestion. Both tolerance and late night or early morning rebound symptoms may develop, necessitating temporary drug withdrawal ("drug holiday") or dose adjustment. An important treatment-associated side-effect of the above mentioned dopaminergic drugs (but not the drugs mentioned below) is "augmentation", which can simply be thought of as paradoxical worsening of RLS due to medications used to treat RLS. More specifically, augmentation refers to progressively earlier occurrence of symptoms (from late evening to early evening, mid-afternoon or even morning), increased symptom intensity, shorter time to recurrence after movement, and spread to the trunk and arms, as well as decreased response to treatment.

Narcotic or opioid medication used to treat pain can also help RLS symptoms. These include mostly older medications: morphine, methadone, codeine, oxycodone, hydrocodone, and propoxyphene. Again no single medication is

consistently better, however in any single patient, one medication may be superior to the others. Possible side effects of these medications include constipation, nausea, and sedation. The biggest concern about using these medications is that their use may cause psychological addiction and physical dependence.

Nevertheless, in cases with very severe RLS, particular in case of augmentation while taking dopaminergic medications, these drugs may be the only option.

Benzodiazepines, which are often used as regular sleeping pills or anxiety medications, are often used for RLS. Common benzodiazepines include diazepam (Valium), clonazepam (Klonopin), alprazolam (Xanax), and lorazepam (Ativan). Our experience is that these medications can help patients fall asleep, but do not help the leg sensations much, except in milder cases. There is also not much scientific evidence that they are very beneficial for RLS.

In recent years, certain medications (or derivatives thereof) initially developed for epilepsy, such as gabapentin (Neurontin), pregabalin (Lyrica), and gabapentin encarbil (Horizant) have emerged as first-line treatment for RLS given their proven long-term effectiveness, safety, and lack of worrisome side-effects such as augmentation. Other antiepileptics, such as carbamazepine (Tegretol), and topiramate (Topamax), may also be of benefit. Of these medications, only gabapentin encarbil (Horizant) has been approved by the FDA specifically for RLS.

Sometimes, combinations of these different types of drugs are needed to control severe symptoms, and often medicines may work for a period of time before needing to be replaced by other medications. The dose of medication and the time at which they are given depend on the duration and intensity of symptoms. In all cases patients should take the lowest dose that controls their individual symptoms. In severe cases associated with low blood iron and refractory to other medications, intravenous iron might be considered but carries a risk of severe allergic reaction (anaphylactic shock).

While RLS is generally not considered a surgical disease, clinicians at BCM have treated one patient with treatment resistant RLS using Deep Brain Stimulation (DBS). DBS is described elsewhere (see “Treatments” on [www.jankovic.org](http://www.jankovic.org)).

Finally, some studies suggest that RLS may spontaneously improve with age.

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### Support Organizations

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