

FAST FACTS AND CONCEPTS #217 RESTLESS LEG SYNDROME

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Background Restless Leg Syndrome (RLS) is a neurologic disorder characterized by unpleasant sensations in the legs causing an uncontrollable urge to move when at rest in an effort to relieve those feelings. Between 2-15% of the population have RLS, with a peak incidence between 40 and 60 years of age and a 1:2 male:female ratio. It occurs more frequently in end-stage renal disease patients on chronic hemodialysis (up to 60%, depending on the series), and in patients with Parkinson's disease (up to 20%) than in the general public. RLS disrupts sleep, can lead to excessive daytime sleepiness, depression, and a decreased quality of life. This *Fast Fact* will review its evaluation and management.

Causes The etiology of primary RLS is unknown although it is thought to be a genetic disorder involving either central or peripheral dopaminergic pathways. Common secondary causes of RLS are polyneuropathies; diabetes mellitus; rheumatologic diseases such as rheumatoid arthritis, Sjogren's syndrome, and fibromyalgia; renal failure; pregnancy; iron deficiency; and hypo- or hyperthyroidism. Drugs including nicotine, caffeine, alcohol, 2nd generation antidepressants such as SSRIs and SNRIs, neuroleptic agents, dopamine-blocking antiemetics such as metoclopramide, and sedating antihistamines are all known to worsen RLS symptoms.

Symptoms and Diagnosis The International RLS Study Group and the National Institutes of Health (NIH) criteria for diagnosis include: (1) an urge to move the legs, (2) temporary relief with movement, (3) onset or worsening of symptoms with rest or inactivity, and (4) worsening or onset of symptoms in the evening or night (3). Patients describe symptoms of trouble falling asleep, trouble getting back to sleep, "a funny feeling in the legs," or a "creepy or crawly feeling in the legs." Patients or their bed partners may also report 'periodic limb movements of sleep': stereotyped, repetitive flexion movements ('jerking') of the legs and occasionally arms, exacerbated when patients lie down for prolonged periods. RLS is a clinical diagnosis for which there is not a confirmatory diagnostic test. It should be differentiated from akathisia, a constant and generalized feeling of motor restlessness not associated with leg discomfort or rest. It can be differentiated from peripheral neuropathies, lumbosacral radiculopathy, and ordinary leg cramps by its circadian rhythm, relief with movement, and the prominence of pain symptoms in non-RLS syndromes.

Treatment Address any treatable secondary causes of RLS (e.g. with iron repletion or levothyroxine) and work with patients to avoid drugs and medications known to aggravate RLS. Distraction activities such as playing video games or crossword puzzles can decrease symptoms during wakeful periods. Drug treatment is recommended for patients who have not improved despite conservative interventions or who have persistent, distressing symptoms. Experts recommend the following (17):

- **Dopamine agonists:** The most frequently used dopamine agonists are pramipexole and ropinirole. Both have been determined to be safe and effective in multiple double-blind, placebo-controlled studies (7-10). Based on the high level of evidence supporting their use, the American Academy of Sleep Medicine recommended both pramipexole and ropinirole as standard therapies for RLS in practice parameters released in 2012 (11). Doses as low as 0.125 mg of pramipexole at bedtime or 0.25 mg of ropinirole are effective in improving sleep and decreasing discomfort in mild-to-moderate cases. Doses of greater than 0.75 mg/day of pramipexole or 4 mg/day of ropinirole are of unproven benefit. Side effects are usually mild, transient, and limited to nausea, lightheadedness, and fatigue. While there are small series showing the effectiveness of levodopa/carbidopa, experts recommend it only be used for intermittent RLS because of worries that levodopa may cause augmentation, rebound, or recurrence of symptoms. Finally, there is one ergot-derived dopamine agonists available: cabergoline. While cabergoline may be useful for patients who have tried and failed pramipexole or ropinirole (11), a similar ergot-derived medication for RLS (pergolide) was associated with heart valve damage and therefore removed from the US market. Because of the potential for a similar concern with cabergoline, it is not recommended as first line therapy.

- Other agents: There are small studies indicating that benzodiazepines (12), opioids (13), and select anticonvulsants such as gabapentin and carbamazepine (14-16) are effective in RLS. Expert opinion, however, generally recommends these drugs as second or third line agents due to the paucity of data supporting their use relative to pramipexole and ropinole.

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Version History: Originally electronically published in July 2009; copy-re-edited by Sean Marks MD in August 2015: references #7-9 and #11 added and incorporated into the text.

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the [Palliative Care Network of Wisconsin](#) (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact's* content. The full set of *Fast Facts* are available at [Palliative Care Network of Wisconsin](#) with contact information, and how to reference *Fast Facts*.

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