CHAPTER **45**

RESTLESS LEGS SYNDROME: Latest Treatment Option and New Thoughts on Cause

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First described more than 350 years ago, restless legs syndrome (RLS) is a neurologic disorder characterized by the intensely uncomfortable and irresistible urge to move the legs. These symptoms often are accompanied by unpleasant pins and needles/prickly sensations in the lower extremities, which typically are worse in the evening and often wake patients from sleep. Patients report that their symptoms are temporarily relieved by walking or moving their legs. This condition can cause major disruptions in normal sleep patterns leading to daytime somnolence, fatigue, and depression thus negatively impacting quality of life in those affected.[1] Epidemiology studies have reported this condition affecting 2.5-15% of the general population.[1-3] Prior Podiatry Institute *Update* publications have thoroughly discussed the clinical features, differential diagnosis, and laboratory findings associated with this condition and the reader is referred to those articles for a more comprehensive review of the syndrome.[4] This article will summarize the major research developments and treatment options that have occurred over the last year in regard to this condition.

RECENT RESEARCH

Two independent studies published in August 2007 found an association between RLS and a nucleotide sequence variant located on chromosome 6p.[5,6] These findings are important in that they lend credence to the theory that RLS has a genetic cause. In the report published by Stefansson et al, an association was found in people who experienced periodic limb movements in sleep, an associated clinical finding found in the majority of patients with RLS, and a specific nucleotide sequence variant on chromosome 6p. The association was found in 2 separate study groups, one from Iceland, and a second group from Atlanta.[5] In a simultaneously reported study by Winkelman et al, researchers found an association between RLS and 3 other genes. One of the genes identified was the same sequence variant on chromosome 6p identified in Stefansson's study making this finding more definite.[6] Interestingly, chromosome 6 is involved in fetal limb development. A secondary finding in the Iceland study was that serum ferritin levels were noted to be reduced in those with the gene variant linked to periodic limb movements in sleep. They concluded that this inverse correlation of the nucleotide sequence variant with iron stores is consistent with the suspected involvement of iron depletion in the pathogenesis of the disease.[5] Iron is necessary in the production of dopamine in the brain, and may explain why recent therapies which increase dopaminergic activity in the brain have shown such promise in treating those with RLS. These recent findings offer hope that the pathophysiology of RLS will be understood, leading to more efficient diagnosis and treatments.

LATEST TREATMENT OPTION

The Food and Drug Administration approved a second drug for treatment of RLS in November 2006. Mirapex (pramipexole) is a dopaminergic agent originally used to treat Parkinson's Disease. It joins Requip (ropinirole) as an effective choice for those with primary RLS whose symptoms are moderate to severe and who experience those symptoms daily. The dosage for Mirapex is 0.125-1.5 mg/day. Both drugs require a titration up to an effective dose, and achievement of the effective dose titration may be more rapid with Mirapex versus Requip.[7,8] Side effects of these drugs include tiredness, headache, nausea, falling asleep unintentionally, dizziness, and sweating. Also impulse control disorders and compulsive behaviors also have been associated with use of these medications. These medications are noted to be most effective in those who have periodic movements in sleep (unintentional recurrent dorsiflexion of the foot and leg) versus those who do not have this associated clinical finding.

A thorough treatment algorithm is presented in the January 2007 issue of *The American Journal of Medicine*[9] and the reader is referred to this source when deciding to initiate treatment for RLS. An accurate diagnosis of RLS must first be established prior to initiating treatment because the disease has many clinical mimics (peripheral neuropathy, nocturnal leg cramps, neuroleptic-induced akathisia, or peripheral vascular disease). Any other underlying condition known to exacerbate RLS also must be addressed and treated if feasible (i.e. anemia, uremia, or pregnancy).

It is important to realize that many patients report

improvement in their symptoms without the use of pharmacologic agents. Nonpharmalogic treatments include elimination of agents known to precipitate RLS (dopamine-blocking agents, antidepressants, antihistamines, caffeine, nicotine, and alcohol) utilizing good sleep practices such as regular bed times and wake times, avoidance of using the bed for anything other than sleeping, and avoidance of stimulating activities such as exercise immediately prior to bedtime. If these treatments are ineffective, pharmacologic agents may be considered. Common medications and their dosages are listed in Table 1.

In summary, 2007 has been an exciting year in regard to advances in understanding causes and treatments for restless legs syndrome. Future *Update* articles on this topic will be presented as new information becomes available.

Table 1

DOSE RANGES OF COMMON MEDICATIONS FOR RESTLESS LEGS SYNDROME*

DRUG CLASS	DOSE RANGE (MG)
Dopaminergics	
Levodopa (with decarboxylase inhibitor)	100–200
Ropinirole	0.25–6
Pramipexole	0.125–1
Pergolide	0.05–0.75
Cabergoline	0.5–4
Opioids	
Codeine (usually in compound)	15–120
Propoxyphene HCl	65–520
Oxycodone	5–20
Hydrocodone	5–20
Tramadol	50–400
Methadone	5–40
Anticonvulsants	
Gabapentin	300–2,700
Sedative-hypnotics	
Clonazepam	0.5–2
Flunazepam	15–60

*Adapted from ref. 10 and 11.

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