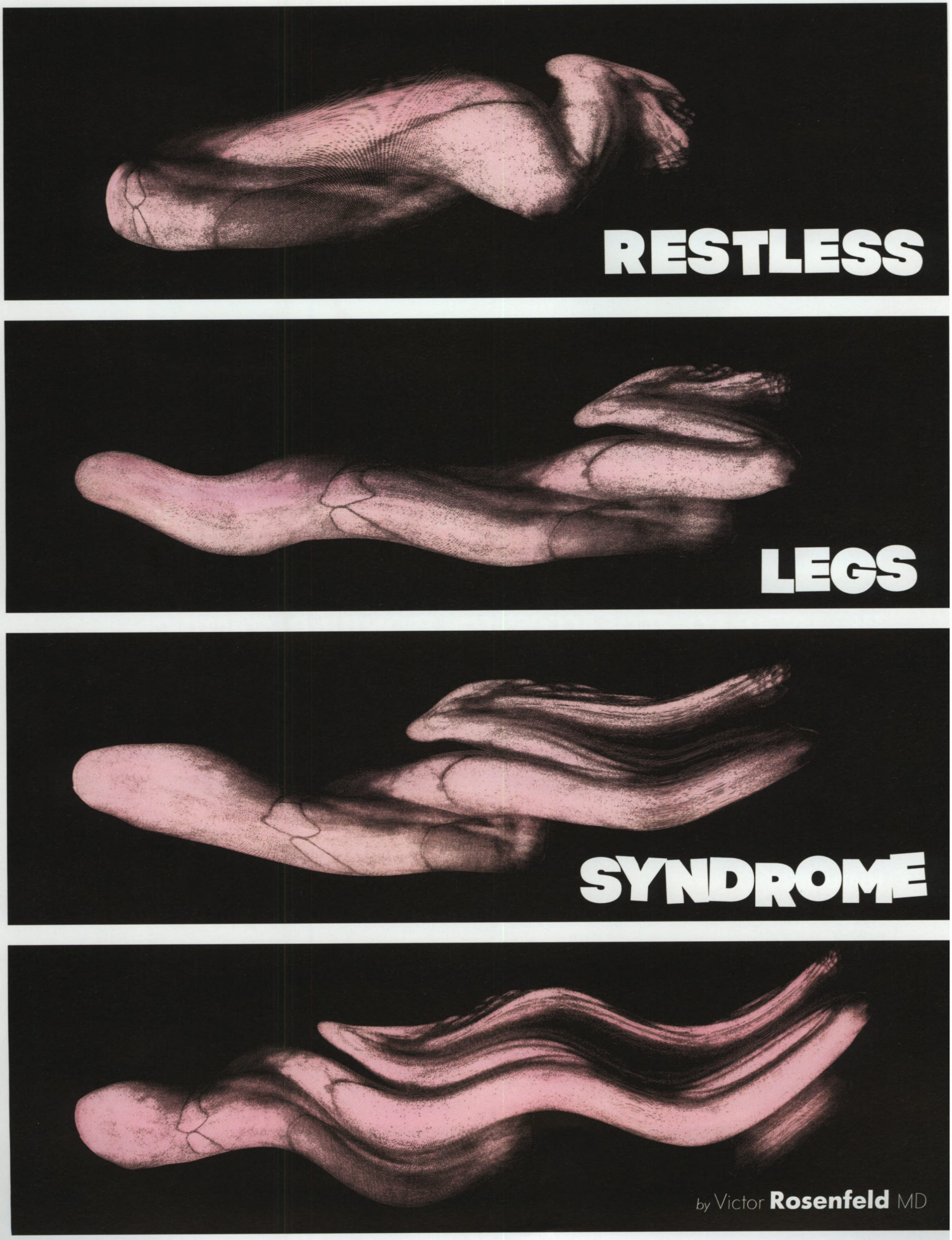
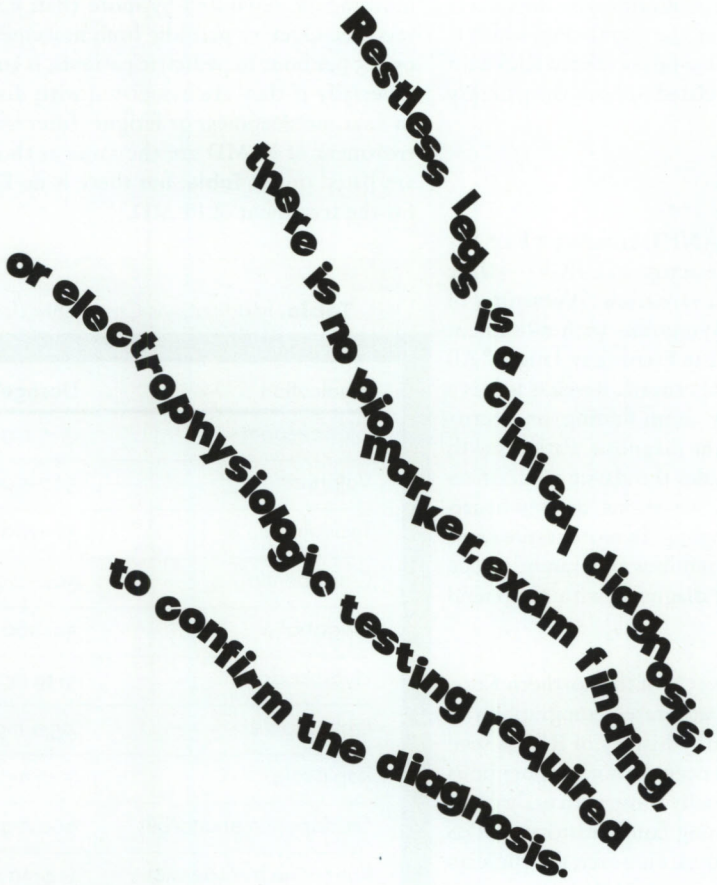

RESTLESS
LEGS
SYNDROME
by Victor Rosenfeld MD




**abstract:** Restless legs syndrome is a common disorder seen in approximately 15% of the population. It can have a myriad of symptoms and is diagnosed on clinical grounds established by the National Institutes of Health. This article focuses on the history, pathophysiology, and diagnosis of restless legs syndrome, as well as the genetics, epidemiology, laboratory, and other testing that can be used in its workup.

## History of Restless Legs Syndrome

The original description of restless legs syndrome (RLS) probably dates back to 1652. Sir Thomas Willis, a physician and neuroanatomist most famously associated with the cerebral vascular term Circle of Willis, described "Night-Crawler Syndrome" or akathisia.[1] It was later discussed by Dr. Karl Axel Ekbom who coined the term RLS in the 1950s.[2] Ekbom produced extensive publications on the subject and predicted an incidence of 5% to 15% of the population, which is in line with what we think today. In addition he correlated RLS with iron deficiency, which we know now is related to both the primary and secondary pathogenesis of RLS.[3-5]

## Clinical Symptoms and Criteria

The current National Institutes of Health (NIH) criteria for RLS has 4 cardinal symptoms, remembered by the acronym URGE—**U**rge to move legs associated with unpleasant sensation. Worsening of symptoms with **R**est. Improvement of symptoms with movement or **G**etting up. Symptoms tend to increase in **E**vening and night.[6] All 4 must be positive for patients to meet the criteria. Restless legs is a clinical diagnosis; there is no biomarker, exam finding, or electrophysiologic testing required to confirm the diagnosis. Patients with RLS describe many other symptoms besides the classic restlessness and need to move, such as creepy-crawly sensations, or even neuropathic symptoms such as burning and tingling. In more severe cases symptoms can also include the upper extremities and, rarely, can be lateralized confounding the differential diagnosis with peripheral and central nervous system diseases.

In current studies, approximately 10% to 15% of the northern European population suffers from RLS, but accurate demographics in other populations are not yet clear.[7] Family history of RLS is seen in approximately 50% of patients and can occur in both a sporadic as well as autosomal dominant pattern.[8] Usually those with early onset symptoms, before age 45, will have a strong family history of RLS and tend to have more pronounced symptoms. However, the clinician will need to be vigilant for the secondary causes of RLS that can be tested and treated accordingly and will be discussed below.

## Testing

As previously mentioned, RLS is a clinical diagnosis and does not require any formal testing. It has been suggested that RLS can be "tested" by using the suggested immobilization test, or SIT, a polysomnogram format utilizing leg electromyogram (EMG) leads during the day for 1 hour. The subject sits comfortably awake and upright in bed with legs outstretched. RLS is supported when more than 40 periodic leg movements of wake occur per hour. Though it may appear on sleep board questions, SIT is not commonly used in clinical practice to diagnose RLS, as it is not required to fulfill current diagnostic criteria.

Restless legs is frequently confused with periodic limb movement disorder (PLMD). PLMD is not synonymous with RLS nor is it necessary for the diagnosis. PLMD can be seen in 80% to 90% of the polysomnograms in patients with a history of RLS during an overnight sleep study.[9] However, PLMD may or may not be clinically relevant as patients with PLMD may not suffer with RLS symptoms and, vice-versa, patients with RLS may not have PLMD seen on a sleep study. PLMD involves excessive movement during sleep. Polysomnography scoring criteria for PLMD requires stereotyped limb movements that are over .5 seconds, at least 4 movements, separated by more than 5 seconds, for less than 90 seconds. Over 15 periodic limb movements per hour in adults, or over 5 per hour in pediatric patients, is considered to be significant, especially if they are associated with disturbed sleep or resulting in daytime sleepiness or fatigue. Interestingly medications for the treatment of PLMD are the same as those used to treat RLS and are listed in the **Table**, but there is no FDA-approved medication for the treatment of PLMD.

**Table.** Medications Commonly Used in RLS and PLMD

| Medication | Dosage* |
|---|---|
| Clonazepam | .5–2 mg |
| Valproate | 500–2000 mg |
| Topiramate | 50–200 mg |
| Gabapentin | 300–1200 mg |
| Pregabalin | 50–200 mg |
| Hydrocodone | 5–10 mg |
| Pramipexole | .25–1 mg |
| Ropinirole | .5–3 mg |
| Gabapentin enacarbil | 600 mg at 6 PM |
| Rotigotine transdermal | 1–4 mg daily |

*every night at bedtime unless otherwise indicated

Occasionally EMG/nerve conduction testing for peripheral neuropathy or lumbar radiculopathy is performed especially if the physical exam suggests focal neurologic deficits or if symptoms have a predominantly neuropathic quality. If RLS and PLMD coexist, or if the clinician is specifically concerned about PLMD without RLS, then overnight polysomnography in a sleep lab should be considered.

Though B12 or hemoglobin labs are recommended in patients with neuropathic complaints, all patients with RLS should be screened for iron deficiency. Consequently, it is recommended that all patients with RLS have iron saturation and ferritin studies performed. If a patient is iron deficient or if ferritin is <50 ug/L, iron supplementation is recommended. Iron levels should be optimized prior to any other treatment being initiated.[10]

"...all patients with RLS should be screened for iron deficiency."

## CAUSES OF RLS

As mentioned, Ekbom associated iron deficiency with RLS. Common causes of secondary RLS include pregnancy, gastric surgery, iron deficiency anemia, and end-stage renal disease. RLS has also been associated with thyroid disease, peripheral neuropathy, lumbar radiculopathy, ADHD, and fibromyalgia, though these latter cases are thought to mimic RLS due to neurologic causes rather than representing true RLS pathology.

Differential diagnoses of RLS include:

- **Positional discomfort**
- **Sleep starts (hypnic jerks)**
- **PLMD**
- **Sleep-related leg cramps**
- **Peripheral neuropathy**
- **Lumbar radiculopathy**
- **ADHD**
- **Fibromyalgia**

The first clues as to the cause of primary RLS came from the treatment of Parkinson's patients with dopa agonists. Many patients with Parkinson's disease given dopa agonists, even in very small dosages, reported a significant improvement of their lower extremity akathisias and RLS symptoms. Dopa agonists were then used off label for RLS in patients without Parkinson's disease with similarly low dosages and similar benefit. Shortly thereafter pramipexole and ropinirole were FDA approved for RLS.

We now know that the rate limiting reaction for dopamine synthesis is tyrosine hydroxylase for which iron is the critical cofactor. It is thus considered that primary RLS may represent a central nervous system form of iron deficiency which is bypassed by the use of dopa agonist. It is also thought that iron deficiency may reduce dopamine receptor DA2 type binding sites in the central nervous system. Postmortem studies have shown abnormalities in the substantia nigra with reduced ferritin and iron transporters.[11] This helps explain why dopamine agonist helps RLS symptoms and why dopamine antagonism will worsen RLS symptoms.

A number of gene foci, such as those located on chromosome 12q (French families), chromosome 14q (Italian families), and chromosome 9p (American families), have been linked to RLS. Other gene foci associated with RLS are located on chromosome 20p (French Canadian), chromosome 2p (South Tyrol), and also chromosome 16p (also French Canadian).[12-18]

## TREATMENT

Treatment usually begins after the 4th decade of life, but in patients with a strong family history treatment frequently is sought earlier. Over-the-counter approaches can include quinine (260 mg every night at bedtime) or a glass of tonic water. Magnesium in higher doses (500 to 1000 mg per day) can also be helpful though GI upset is common with the salt forms of magnesium; magnesium malate or gluconate is usually recommended. Lack of exercise, obesity, and tobacco use are associated with RLS. Exercise and other lifestyle changes are typically recommended.

Iron replacement should always be performed if ferritin or iron saturation are low. Typically patients will respond to oral iron supplementation, but in many cases IV iron infusions are necessary to keep ferritin levels >50 ug/L.[19] The most commonly used medications for RLS include benzodiazepines, anticonvulsants, narcotics, muscle relaxants, and dopa agonists (see **Table**). Levodopa/carbidopa (Sinemet®) may encourage "anticipation," where patients experience their symptoms earlier and earlier during the day, and is therefore not considered first-line therapy at this time.[20] Two newer medications recently FDA approved for RLS, gabapentin enacarbil and the rotigotine transdermal system, are particularly effective.

Gabapentin enacarbil extended release (Horizant®) is available in only 1 dose, 600 mg, and is recommended to be taken at 6PM, a few hours before sleep. It is well tolerated and effective. Most common side effects of gabapentin enacarbil extended release include sedation, dizziness, headache, fatigue, and nausea.[21] Rotigotine transdermal system (Neupro®) is a dopa agonist that is available in 1, 2, 4, 8 mg patches, used daily, and is very effective in the treatment of RLS. In my experience, there is lower incidence of side effects using the transdermal system effect compared to the oral dopa agonists. Most common side effects of rotigotine transdermal system include local site reactions, nausea, somnolence, and headache. Gambling and other addictive behaviors which can be seen with the oral dopa agonists have not as yet been described with the rotigotine transdermal system.[22]

A common cause of referral to a sleep center for treatment of RLS is iatrogenesis, as many prescription as well as OTC medications can exacerbate RLS symptoms. Since we know that dopa agonism helps RLS, it is understandable that dopamine antagonists, commonly used to treat mood and behavior disorders, will induce symptoms. Any medication that significantly increases the activating neurotransmitters (such as serotonin, norepinephrine, and dopamine) and activating neuromodulators (such as histamines) can also exacerbate RLS symptoms. Consequently the use of OTC sleep aids and allergy medicines that contain antihistamines are the most common causes of induced or exacerbated RLS. Most antidepressants, including tricyclics (amitriptyline), serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine), and serotonin specific reuptake inhibitors (sertraline, paroxetine) are all associated with RLS exacerbation.[23,24]

In May of 2014, the FDA approved the first topical device for the treatment of RLS. The "relaxis" is a noninvasive, and nonpharmaceutical device that the patient lays on in bed which produces vibration that gradually ramps up then down over 30 minutes. It was found to be superior to placebo in 2 controlled trials. Side effects may include worsening of RLS symptoms. It will be available by prescription only.[25,26]

## CONCLUSION

RLS is a clinical diagnosis made by applying the NIH URGE criteria and is a common condition. Overnight polysomnography is not required to make the diagnosis. Iron metabolism is involved with the disease process, and a number of genes have been identified. Dopa agonists and gabanoids are FDA approved for therapy. ◘


**References**

1. Willis T. *The London Practice of Physick, or the Whole Practical Park of Physick.* London, England: Thomas Basset and William Crook; 1685.

2. Ekbom KA. Restless legs. *Acta Med Scand.* 1945;158:1–123.

3. Ekbom KA. Restless legs syndrome. *Neurology.* 1960;10:868–873.

4. Ekbom KA. Asthenia crurum paraesthetica (irritable legs). *Acta Med Scand.* 1944;118:197–209.

5. Ekbom KA. [Restless legs in blood donors]. *Sven Läkartidn.* 1956;53:3098–3103.

6. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. *Sleep Med.* 2003;4:101–119.

7. Allen RP, Stillman P, Myers AJ. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in western Europe: prevalence and characteristics. *Sleep Med.* 2010;11(1):31–37.

8. Hening W, Walters AS, Allen RP, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* 2004;5:237–246.

9. Coleman RM. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. *Sleeping and Waking Disorders: Indications and Techniques.* Menlo Park, CA: Addison-Wesley; 1982:265–295.

10. Mizuno S, Mihara T, Miyaoka T, et al. CSF iron, ferritin and transferrin levels in restless legs syndrome. *J Sleep Res.* 2005;14:43–47.

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

12. Winkelmann J, Polo O, Provini F, et al. Genetics of restless legs syndrome (RLS): state-of-the-art and future directions. *Mov Disord.* 2007;22(suppl 18):S449–458.

13. Winkelmann J, Schormair B, Lichtner P, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nat Genet.* 2007;39:1000–1006.

14. Pichler I, Hicks AA, Pramstaller PP. Restless legs syndrome: an update on genetics and future perspectives. *Clin Genet.* 2008;73:297–305.

15. Winkelmann J, Lichtner P, Schormair B, et al. Variants in the neuronal nitric oxide synthase (nNOS, NOS1) gene are associated with restless legs syndrome. *Mov Disord.* 2008;23:350–358.

16. Lohmann-Hedrich K, Neumann A, Kleensang A, et al. Evidence for linkage of restless legs syndrome to chromosome 9p: are there two distinct loci? *Neurology.* 2008;70:686–694.

17. Young JE, Vilarino-Guell C, Lin S-C, et al. Clinical and genetic description of a family with a high prevalence of autosomal dominant restless legs syndrome. *Mayo Clin Proc.* 2009;84:134–138.

18. Levchenko A, Montplaisir J-Y, Asselin G, et al. Autosomal-dominant locus for restless legs syndrome in French-Canadians on chromosome 16p12.1. *Mov Disord.* 2009;24:40–50.

19. Wang J, O'Reilly B, Venkataraman R, et al. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: a randomized, double-blind, placebo-controlled study. *Sleep Med.* 2009;10(9):973–975.

20. Happe S, Trenkwalder C. Role of dopamine receptor agonists in the treatment of restless legs syndrome. *CNS Drugs.* 2004;18:27–36.

21. Kushida CA, Becker PM, Ellenbogen AL, et al, for the XP052 Study Group. Randomized, double-blind, placebo-controlled study of XP13512/GSK 1838262 in patients with RLS. *Neurology.* 2009;72:439–446.

22. Trenkwalder C, Benes H, Poewe W, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2008;7:595–604.

23. Ondo WG. Restless legs syndrome. *Curr Neurol Neurosci Rep.* 2005;5:266–274.

24. Ondo W. Secondary restless legs syndrome. In: Ray Chaudhuri K, Odin P, Olanow CW, eds. *Restless Legs Syndrome.* London, England: Taylor & Francis; 2004:57.

25. Burbank F, Buchfuhrer MJ, Kopjar B. Sleep improvement for restless legs syndrome patients. Part 1: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms. *J Parkinsonism Restless Legs Syndrome.* 2013;3:1–10.

26. Burbank F, Buchfuhrer MJ, Kopjar B. Improving sleep for patients with restless legs syndrome. Part II: meta-analysis of vibration therapy and drugs approved by the FDA for treatment of restless legs syndrome. *J Parkinsonism Restless Legs Syndrome.* 2013;3:11–22.