

Restless Legs Syndrome

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Background: Restless legs syndrome is a common but not well-recognized central nervous system disorder that leads to insomnia and daytime distress.

Methods: A MEDLINE search of the recent English language literature was undertaken with review of appropriate articles and references.

Results: A growing body of work has added to an understanding of the epidemiology, diagnostic criteria, appropriate evaluation, and effective management of restless legs syndrome.

Conclusions: Restless legs syndrome occurs in about 6% of the adult population, more so in the elderly. Affected patients experience uncomfortable sensations in the legs with inactivity, more pronounced late in the day and at bedtime, which are temporarily relieved by moving the limbs. Affected patients can suffer from insomnia, disrupted sleep, daytime fatigue, and difficulty with sedentary activities. Most cases are idiopathic, although secondary causes, such as iron deficiency, should be excluded. Dopaminergic agents are highly effective in treating restless legs syndrome, but side effects can be problematic. Alternative medications include benzodiazepines, opioids, gabapentin, and clonidine. (J Am Board Fam Pract 2001;14:368–74.)

Wherefore to some, when being a Bed they betake themselves to sleep, presently in the Arms and Leggs Leapings and Contractions to the Tendons, and so great a Restlessness and Tossing of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest Torture.

—Sir Thomas Willis
English physician, 1672

Restless legs syndrome, “the most common disorder you’ve never heard of,”¹ is an uncomfortable sensation in the legs, typically occurring with inactivity, especially around bedtime. Although Ekbom described restless legs syndrome more than 50 years ago, physicians and the lay community remained largely unaware of the disorder until fairly recently.

The past decade has seen a marked increase in familiarity with restless legs syndrome, with a corresponding increase in research activity and knowledge. A 1994 article in *Modern Maturity* generated more than 2,600 responses from readers who finally

had a name for the symptoms they were experiencing.¹ A 1999 task force from the American Academy of Sleep Medicine summarized the current understanding of restless legs syndrome² and published associated practice parameters.³ More recently, a collaborative working group from the National Institutes of Health published a primary care-oriented review aimed at improving detection and management of this common disorder.⁴ Family physicians today are in an improved position to recognize restless legs syndrome and to offer more effective treatment.

Methods

A MEDLINE search of the recent English language literature was undertaken with review of appropriate articles and references. Key words used for the search were “restless legs syndrome” and “periodic limb movement.”

Description

Patients with restless legs syndrome experience an intensely uncomfortable sensation in their legs and occasionally in other extremities that compels them to move. This sensation has been described as “creepy crawly, tingling, bubbly” and “like bugs tunneling.” While often quite distressing, the sensation is not normally reported as painful. Symp-

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toms typically appear at rest and are at least temporarily relieved by moving the limbs. Characteristically following a diurnal variation, the symptoms worsen later in the afternoon and evenings, particularly at bedtime.

Most patients with restless legs syndrome also experience periodic limb movements of sleep.⁵ These movements involve a periodic, stereotypical Babinski-like flexion of the legs, with extension of the foot and toe, which occurs during sleep. Periodic limb movements of sleep typically occur in clusters throughout the night, with a periodicity of 20 to 40 seconds. Patients whose periodic limb movements of sleep are associated with arousal and disrupted sleep sufficient to cause daytime drowsiness are said to have periodic limb movement disorder.

Although mild in some patients, the symptoms of restless legs syndrome and periodic limb movements of sleep can cause intense suffering in others. A common source of distress is insomnia. Affected patients might come to dread bedtime, as the late hour and inactivity combine to produce severe symptoms. Patients might report seeking relief by pacing the floors in the middle of the night, only to have their symptoms return as soon as they collapse, exhausted, back to bed. Even after patients are able to achieve sleep, patients with periodic limb movement disorder might find that sleep is unrestorative and of poor quality.

Patients with restless legs syndrome are often troubled by similar daytime symptoms as well. Sedentary activities might be difficult. Travel by car or airplane can be uncomfortable. Patients might be unable to sit through classes or meetings or to work in a seated position for any length of time.

Epidemiology

Restless legs syndrome is a common disorder, although a precise figure for prevalence has been hard to establish. Variations in diagnostic criteria and study methodology have produced results ranging between 2% and 15% of the adult population,^{6,7} with 6% recently suggested as a reasonable estimate.⁸ Although symptoms in young children are relatively rare, the disorder is common in older adults. Recent studies in those older than 65 years have found that between 10% and 28% are affected.^{9,10} The severity of symptoms tends to increase with age as well, so that this disorder is of

particular clinical importance in geriatric patients. Restless legs syndrome can run in families, with more than two thirds of affected patients reporting a positive family history.¹¹

Cause

The cause of restless legs syndrome and periodic limb movements of sleep is not known. A possible mechanism for the production of symptoms involves disinhibition of normal central nervous system pacemakers. Clinical and laboratory evidence supports a primary role of the dopaminergic system in these disorders, with contributing influences of opioid and other neurotransmitters.¹² Despite shared neurochemical features, however, current evidence does not support the concept that patients with restless legs syndrome are at any increased risk for developing Parkinson disease.¹³

Both restless legs syndrome and periodic limb movements of sleep are reported more frequently by patients with certain medical conditions than they are in the general population. Iron deficiency, even at levels insufficient to cause anemia, can be associated with restless legs syndrome.¹⁴ Dialysis patients are often affected, with studies reporting a prevalence of 20% to 57% in this population.¹⁵ Restless legs syndrome symptoms appear to be unaffected by dialysis but are often relieved after renal transplantation.¹⁶ Symptoms are also more common during pregnancy. One survey of 500 patients found that 19% reported restless legs syndrome symptoms during pregnancy, that 7% described these symptoms as "severe," and that resolution of symptoms occurred in 96% of affected patients within 1 month of delivery.¹⁷ Increased prevalence of restless legs syndrome symptoms has been reported in patients with hypothyroidism and diabetes, although these associations have not been extensively studied and might represent coincidental comorbidities.² Increased symptoms have also been associated with decreased magnesium¹⁸ and folate levels.¹⁹ A small case series found that patients with prominent leg varicosities had an increased incidence of restless legs syndrome symptoms, and that many patients experienced improvement after sclerotherapy.²⁰

Diagnosis

Restless legs syndrome is diagnosed through a careful history. Patients should describe symptoms that

Table 1. International Restless Leg Syndrome Study Group Criteria for Diagnosis of Restless Leg Syndrome.

A desire to move the limbs usually associated with paresthesias or dysesthesias
Motor restlessness (during wakefulness patients move the limbs in an attempt to relieve the discomfort)
Symptoms worse or exclusively present at rest with at least partial and temporary relief by activity
Symptoms worse in the evening or night

From Hening et al.²

are worse in the evening, are most pronounced at rest, and are at least temporarily improved by moving the affected limbs (Table 1).

Conditions that might mimic restless legs syndrome should be excluded, including anxiety, drug-induced akathisia, peripheral neuropathy, leg cramps, and tic disorders.⁸

Periodic limb movements of sleep is a sleep phenomenon and, like snoring, cannot be noticed by the sleeping patient. The diagnosis can be suggested from the reports of a patient's bed partner but can only be formally established by polysomnography. Reports of periodic, abrupt leg movements should be differentiated from hypnic jerks, which occur briefly just as a patient is falling asleep.

Although most cases of restless legs syndrome are idiopathic, it is important to search for secondary causes or exacerbating factors and address these causes, when possible. Intake of alcohol, caffeine, and nicotine should be documented and minimized.

Serum ferritin levels should be obtained; levels less than 50 ng/mL have been associated with restless legs syndrome, even in the absence of decreased hemoglobin or serum iron levels.^{21,22} A study of cerebral spinal fluid in 16 patients with restless legs syndrome found markedly lower ferritin levels than in those of healthy age-matched controls.²³ A recent randomized, double-blind, placebo-controlled trial of iron supplementation involving 28 patients with restless legs syndrome, only some of whom were iron-deficient, did not show a measurable benefit. Both of the recent consensus statements recommend a trial of iron replacement in patients with restless legs syndrome in whom iron deficiency has been documented.^{3,4}

Serum glucose and creatinine should be measured.^{3,4} Some evidence supports obtaining thyroid-stimulating hormone, magnesium, and folate

Table 2. Physician and Patient Resources for Restless Leg Syndrome.

Restless Legs Syndrome Foundation, Inc.
 4410 19th Street, NW, Suite 201, Rochester, MN 55901
 Patient hotline: (877)INFORLS
 Online and published information on restless leg syndrome for physicians and patients: www.rls.org
 Quarterly newsletter: *Night Walkers*
 Support groups

Worldwide Education and Awareness for Movement Disorders (WE MOVE)

204 W 84th Street, New York, NY 10024
 Telephone: (800)437-MOV2
 Detailed online information on restless leg syndrome for physicians and patients: www.wemove.org
 Newsletter: *We Talk*

levels as well. Classical neuroleptic and many antidepressant medications can exacerbate symptoms.²⁴⁻²⁶ Affected patients could benefit from medication changes, including a switch to antipsychotic medications with fewer extrapyramidal side effects, and trials of alternative antidepressants.²⁷

Treatment Approaches

Not all patients with restless legs syndrome need medication. Many patients will benefit from appropriate sleep hygiene practices, including avoiding caffeine, nicotine, and alcohol. Consistent, relaxing bedtime routines are helpful. Vigorous exercise and stimulation, including sexual activity, can worsen symptoms if they occur within 1 or 2 hours of bedtime. Because sleep deprivation can worsen restless legs syndrome symptoms, which can in turn lead to further sleep deprivation, patients should allow themselves adequate opportunity for sleep in their daily schedules.²⁸ Patients might find it helpful to make adaptive changes, such as working at a high desk with a stool, taking an aisle seat on trips or in meetings, and shifting their sleep cycle to permit a later awakening time.

Several potentially important but not rigorously tested nonpharmacologic therapies have been used in restless legs syndrome, including massage, electroencephalographic biofeedback, counterirritants, and acupuncture.² Much of the information regarding these and other modalities is disseminated informally, through newsletters, support groups, and the Internet (Table 2). Patients might find it

Table 3. Medications Used to Treat Restless Legs Syndrome.

Drug	Dosage Range
Dopaminergic agents	
Carbidopa/levodopa	
Regular formulation (Sinemet)	12.5/50 mg before bed to 25/100 mg three times a day
Sustained release (Sinemet CR)	25/100 mg before bed to three times a day
Pergolide (Permax)	0.05–1.0 mg in 2 doses (dinner and 1 hr before bed)
Pramipexole (Mirapex)	0.125 mg before bed to 1.0 mg three times a day
Ropinirole (Requip)	0.25 mg before bed to 3 mg three times a day
Benzodiazepines	
Clonazepam (Klonopin)	0.5–2.0 mg before bed
Opioids	
Propoxyphene	65–130 mg three times a day
Codeine	15–30 mg four times a day
Oxycodone (Percocet)	5–10 mg four times a day
Tramadol (Ultram)	50 mg four times a day
Others	
Gabapentin (Neurontin)	100–800 mg three times a day
Clonidine (Catapres)	0.1 mg before bed to 0.3 mg twice a day

helpful to explore these resources to learn more about this chronic disorder and how to cope with it.

Although medications used in restless legs syndrome have been more extensively studied than have nondrug therapies, much of the evidence base that supports current recommendations remains relatively weak. Many published studies describe small case reports or clinical trials that are not randomized, not blinded, or involve few patients. Studies that have involved placebos often show a strong placebo effect in this disorder.²⁹ Nevertheless, a combination of clinical experience and published studies supports a number of evidence-based recommendations regarding the use of medications to treat restless legs syndrome symptoms. A decision to use medications should take into account the severity of the patient's symptoms and functional impairment and a knowledge of the side effects and difficulties associated with various pharmacologic agents (Table 3).

Dopaminergic Agents

Dopaminergic agents, as a rule, are highly effective in treating the symptoms of restless legs syndrome and periodic limb movement disorder. In fact, a lack of response to a moderate dose of a dopaminergic agent might lead one to question seriously the diagnosis. Unfortunately, these agents frequently cause challenging side effects. Many dopaminergic agents have a rebound phenomenon, with

a tendency for symptoms to increase as a dose wears off, so that a patient experiences disruptive symptoms during the night or early morning. A related phenomenon, augmentation, involves an increase in symptom intensity, earlier daily onset of symptoms, decrease in medication efficacy, or expansion of symptoms to other parts of the body.³⁰ Increasing medication dosage typically leads to further worsening of rebound and augmentation once they occur. These side effects usually disappear once the offending agent is discontinued.

Carbidopa-levodopa (Sinemet) has been the most frequently used agent for initial treatment of restless legs syndrome.² Therapy may be started with a very low dose, such as one half of a 25/100-mg tablet taken 1 hour before bedtime, and titrated upward until the desired effect is reached. The patient might need to take a second dose during the night. An alternative regimen involves combining the usual bedtime dose with an additional low dose, typically 25/100 mg of the long-acting formulation (Sinemet CR). Patients might need additional doses to control daytime symptoms. Total daily dose of levodopa above 200 mg should be prescribed with caution to avoid augmentation, which has been reported in more than 50% of patients with restless legs syndrome who take this medication.³⁰

The dopamine agonists bromocriptine (Parlodel) and pergolide (Permax) are also effective in

treating restless legs syndrome. Pergolide, the more commonly used of the two drugs, appears to cause less augmentation than is observed with levodopa, particularly when higher doses are required.^{31,32} An open-label trial of pergolide in 15 patients with severe restless legs syndrome who had previously experienced augmentation of symptoms while on levodopa found that all patients experienced some degree of improvement while taking an average of 0.4 mg of pergolide per day. None of these patients reported serious augmentation during the 6-month period of observation.³¹ A randomized, double-blind, placebo-controlled study of 16 patients with restless legs syndrome who took an average 0.35 mg of pergolide per day found a 61% global improvement in the treatment group compared with 19% in those patients taking placebo.³² No rebound or augmentation of restless legs syndrome symptoms was reported, but the 3-week duration of the trial limits the importance of this observation. Another study started with patients taking levodopa and successfully switched many patients who experienced augmentation to pergolide.³³ Because of side effects – gastrointestinal distress, hypotension, and nasal stuffiness – pergolide needs to be started at a low dose and slowly adjusted upward.

Two newer dopamine agonists, pramipexole (Mirapex) and ropinirole (Requip), have also been found helpful in treating restless legs syndrome,^{34,35} although there are less experience and fewer clinical trials involving these medications to date. Although the dopamine agonists are currently considered to be second-line agents after failure of carbidopa-levodopa therapy, as experience with and knowledge of these promising drugs increases, they could become medications of first choice.

Benzodiazepines

The benzodiazepines have nonspecific sleep-promoting properties. Whether they also have a specific effect on restless legs syndrome and periodic limb movement disorder is unclear.² Clonazepam (Klonopin) is the best-studied benzodiazepine for this disorder, but other medications in this class have been used as well. Benzodiazepines could be a satisfactory choice in treating restless legs syndrome symptoms that are relatively mild and primarily sleep related.⁸ Side effects of daytime drowsiness, confusion, and unsteadiness might be problematic, particularly in elderly patients. Pre-

scribers and patients also need to be aware of the potential for habituation and dependence with all benzodiazepines.

Opioids

Opioid agents have been shown to be helpful in both restless legs syndrome and periodic limb movement disorder.^{36,37} In addition to their analgesic and sedative properties, they might work through a specific interaction between the opioid and dopaminergic systems. Direct comparisons between various opioids and between opioids and other medications, are lacking. Because of concerns about their addictive potential, these agents are generally reserved for use in more severely affected patients, in patients who have failed other medications, or in the uncommon patient with pain as a prominent symptom.

Other Medications

Anticonvulsant medications have been used with some success in restless legs syndrome. A 1984 double-blind, placebo-controlled study of carbamazepine (Tegretol) in 174 patients showed significant improvement in both the treatment and placebo groups, although there was a demonstrable treatment effect.³⁸ Since then, only two very small open-label trials have been undertaken using carbamazepine in restless legs syndrome that have showed modest benefits. More recently, gabapentin (Neurontin) has been found to have some benefit in treating restless legs syndrome. In an open-label study involving only 8 patients, gabapentin was given in doses ranging from 300 to 2,400 mg/d (mean 1,163 mg/d). Three patients had 76% to 100% improvement in restless legs syndrome symptoms, 1 had 0% to 25% improvement, and the remaining 4 patients experienced no benefit.³⁹ A second open-label series involved 16 consecutive patients who took gabapentin at doses ranging from 300 mg at bedtime to 400 mg given 5 times a day. All patients reported at least a 50% improvement in restless legs syndrome symptoms.⁴⁰

Although these anticonvulsants might have a role in treating undifferentiated patients with restless legs syndrome, they might be particularly well-suited for those with neuropathy or considerable pain. Small trials have suggested some improvement of restless legs syndrome symptoms with clonidine (Catapres),⁴¹ which might be appropri-

ately tried in a patient with both restless legs syndrome and hypertension.

Summary

Restless legs syndrome is common and can be particularly important in geriatric patients. Effective management involves excluding or treating secondary causes, consistent sleep hygiene, and judicious use of medications.

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