

## RESTLESS LEGS SYNDROME FOUNDATION, INC.

# Medical Bulletin

**Abstract** | *Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a distressing urge to move the legs and sometimes also other parts of the body, usually accompanied by a marked sense of discomfort or pain in the leg or other affected body part. RLS is triggered by rest or inactivity, and its symptoms are temporarily relieved or suppressed by movement. It follows a circadian pattern, with symptoms most intense in the evening and nighttime hours. The disorder can be relatively mild or may have profoundly disruptive effects on a patient's sleep and daily life. It may be either idiopathic (primary RLS, which often has a familial component) or secondary, occurring in conjunction with other medical conditions, particularly iron deficiency anemia, pregnancy, or end-stage renal disease. It has been argued that iron deficiency represents a primary factor in the development of RLS, and this has*

*been supported by CSF and brain imaging studies. When lifestyle changes and nonpharmacologic therapies fail to sufficiently mitigate RLS, treatment with dopaminergic agents or opioids frequently brings relief. Therapy with select anticonvulsants is of value in some RLS patients. New research with familial RLS has documented two distinct genetic linkages — at 12q in a Canadian family and 14q in an Italian family. RLS appears increasingly to be a complex disorder probably influenced by a variety of genetic factors and other causes that may work through a variety of biochemical systems as well as a number of prominent environmental factors.*



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## Introduction and History of Restless Legs Syndrome

The sensorimotor disorder restless legs syndrome (RLS) was described as early as the late 17th century by the great English anatomist and physician Sir Thomas Willis, who also described the opioid responsiveness of the syndrome.<sup>(1)</sup> For the next two centuries, RLS was mentioned only infrequently in the literature. In the early 1940s, Swedish neurologist Karl Ekbom wrote a series of detailed clinical descriptions of the disorder, and coined the term restless legs syndrome.<sup>(2)</sup> Another major advance came when Lugaresi recorded periodic limb movements in sleep (PLMS) using EMG-recording electrodes attached to the legs of patients with RLS. He documented the very frequent occurrence of PLMS in patients with RLS.<sup>(3)</sup>

The American Sleep Disorders Association developed diagnostic criteria for RLS in the late 1970s, and published practice parameters for the treatment of RLS and periodic limb movement disorder (PLMD) in 1999.<sup>(4)</sup> The International Restless Legs Syndrome Study Group (IRLSSG) delineated the minimal criteria needed for a diagnosis of RLS and associated features commonly seen in patients with the disorder. These criteria were published in the medical literature in 1995<sup>(5)</sup> and were updated and further clarified at a National Institutes of Health workshop in 2002.<sup>(6)</sup> Therapeutic advances were minimal until the latter part of the 20th century, other than the discovery by Ekbom and some contemporaries in the mid-century of the importance of iron therapy.<sup>(7)</sup> In the late 1970s and early 1980s,

treatment with benzodiazepines was reported to be helpful in controlling the symptoms of RLS.<sup>(8,9)</sup>

The past two decades have seen major developments in effective therapies for the symptoms of RLS. Among the most significant of these discoveries was that of Akpinar, who suggested that L-dopa and other dopaminergic agents might be helpful in RLS.<sup>(10)</sup> Numerous well-designed and blinded studies have since documented the importance of this finding, and today several major pharmaceutical companies are exploring the efficacy of dopaminergic drugs for RLS on a worldwide basis. The last 20 years have also produced scientific documentation of Willis's original finding that opioids might be helpful in RLS, along with discovery that the anticonvulsant gabapentin has a major beneficial impact on RLS symptoms.

Recent genetic linkage studies, including those of Montplaisir and Rouleau<sup>(11)</sup> and of Zucconi and Ferini-Strambi<sup>(12)</sup> suggest there may be an important genetic contribution to the disorder. The discovery that RLS is linked to chromosome 12 or 14, depending on the family, offers promise for understanding the pathology of RLS. Positron emission tomography (PET) studies have explored the possible role of dopamine deficiency in the production of RLS symptoms, and electrophysiology studies such as those in the laboratory of Paulus and Trenkwalder<sup>(13)</sup> have sought to locate the area of the brain or spinal cord responsible for the production of PLMS and RLS symptoms. Earley and Allen<sup>(14,15)</sup> have documented central iron deficiency in patients with RLS through MRI and cerebrospinal fluid (CSF) studies.

## Features of Restless Legs Syndrome

In 2002, a collaboration of participants in the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health and members of the International Restless Legs Syndrome Study Group reviewed and revised the diagnostic criteria for RLS, along with supportive clinical features and associated features.<sup>(6)</sup> These criteria are outlined in (Table 1).

### Diagnostic Criteria

#### *Essential criteria*

The following four primary features define RLS and all must be present if the diagnosis is to be made.

1. Urge to move the legs, usually with dysesthesias  
*This urge to move the legs is usually accompanied or caused by uncomfortable and unpleasant sensations in the legs, but may be present without the uncomfortable sensations. Sometimes the arms or other body parts are involved in addition to the legs.*

Some patients describe only an urge to move and are unaware of a sensory component; others cannot separate the urge to move from the uncomfortable sensations and cannot identify a temporal relationship. Most patients who seek medical treatment describe both components. One ongoing study notes that about 10% of family members of people with RLS who also have RLS themselves (albeit often mild disease) report having an urge to move without any other related sensation.<sup>(16)</sup> Patients often have difficulty describing their RLS sensations, and use such broad terms as *uncomfortable* and *inside the leg*, or compare the sensations to

**Table 1 | Features of RLS**

- A. Essential criteria: These primary features must be present for a diagnosis of RLS.
1. *An urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations in the legs (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)*
  2. *The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.*
  3. *The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.*
  4. *The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When the symptoms are very severe, the worsening at night may not be noticeable, but must have been previously present.)*
- B. Supportive clinical features of RLS: Presence of these features may help resolve any diagnostic uncertainty.
1. *Periodic limb movements (during wakefulness or sleep)*
  2. *Family history of RLS*
  3. *Response to dopaminergic therapy*
- C. Associated clinical features: These features may provide additional information about the patient's diagnosis:
1. *Natural clinical course following certain identifiable patterns*
  2. *Sleep disturbance*
  3. *Normal medical evaluation/physical examination*

some other feeling. In general, two themes emerge: the sensations are perceived to originate deep inside the leg, and to involve a sense of movement within the leg.

A complaint of pain has traditionally been believed to exclude the diagnosis of RLS, but new research indicates that many patients with RLS do in fact experience their sensations as painful.<sup>(17,18)</sup> Bassetti and colleagues reported that more than 50% of their 55 RLS patients described pain as a primary component of their RLS.<sup>(17)</sup>

RLS may also involve the arms or other body parts, although the sensations are almost always first noticed in the legs before spreading to involve other areas.<sup>(19)</sup> Estimates of RLS patients with symptoms in the arms range from 34%<sup>(19)</sup> to almost 50%.<sup>(20)</sup> With increasing severity, RLS symptoms may spread to other parts of the body, including the hips, trunk, and even the face, but in such cases the legs continue to be affected.<sup>(17,21)</sup>

The involved area of the leg appears to vary considerably. Even in patients with neuropathy-related RLS, there is no documentation that sensations start in the more-distal part of the leg, where the sensory deficit is likely to be worst,<sup>(22)</sup> nor is any clear pattern of progression reported, except that increasing severity involves the spread of symptoms to a larger area of the leg and to other body parts. Ekblom reported that RLS symptoms almost never involve the foot alone,<sup>(7)</sup> but in rare clinical cases a patient will report symptoms beginning in a foot and progressing to the leg.

The response to an urge to move in RLS must not be confused with habitual repetitive movements such

as foot-tapping. These unconscious motor behaviors are carried out without any acute or distressing awareness of an urge to move.

2. Onset or exacerbation with rest  
*The urge to move and/or unpleasant sensations begin or worsen during periods of rest or inactivity, particularly with lying down or sitting.*

Most evidence in support of this criterion comes from Montplaisir and colleagues, who have studied the effects of immobility on RLS using a suggested immobilization test (SIT).<sup>(20)</sup> The test evaluates periodic leg movements while awake (PLMW) and self-reported sensory symptoms in subjects instructed to remain still for 1 hour while sitting on a bed with their legs outstretched and supported. Compared with controls, patients with RLS exhibit more PLMW and an increase in sensory disturbance during the immobilization period. Their symptoms may be absent in the initial stages of the rest period, but motor and sensory symptoms are increasingly likely to surface with the duration of rest. Intensity of the sensory symptoms and frequency of the periodic leg movements (PLM) also increase as rest progresses.

As used in this criterion, "rest" includes both physical immobility and decreased central nervous system activity leading to reduced alertness. Presumably, both of these factors contribute to the onset of RLS symptoms.<sup>(23)</sup>

Rest with inactivity almost always involves sitting or lying supine, and these positions are specified here to emphasize the characteristic body position during rest. In

general, however, no specific body position causes the symptoms; rather, any rest position — if the resting state lasts long enough — should engender the symptoms. The more restful the position and the longer it lasts, the more likely it is to give rise to RLS symptoms. Pain or discomfort from circulatory compromise or stiffness from prolonged sitting or lying in a fixed position should not be confused with RLS symptoms.

### 3. Relief with movement

*The urge to move or unpleasant sensations of RLS are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.*

Relief with movement usually begins immediately or very soon after activity begins. Relief is not always complete, and even when it is, patients may have an abiding awareness that their RLS symptoms are just barely suppressed and will resume as soon as the movement ceases. The examining clinician should ask whether relief occurs while the patient is actually moving, and should note the immediacy as well as the persistence of relief with physical activity.

As an alternative to movement, a patient may use a counterstimulus, such as rubbing the legs or taking hot or cold baths.<sup>(7)</sup> Winkelmann and colleagues found that changes of temperature represented an effective coping strategy in 82% of 300 patients.<sup>(19)</sup> As their RLS becomes more severe, patients may find that the degree of relief they achieve with movement decreases to the point that no amount of movement or counterstimulation provides relief. When a patient presents with RLS-like symptoms so severe that they

cannot be relieved by movement, he or she should be able to recall that movement brought relief earlier in the course of the disease. This criterion (relief with movement) must be present or have been present in some form in order for a diagnosis of RLS to be made; in severely affected patients, however, it may become attenuated, and may only be available as a remnant or as an historical feature.

### 4. Circadian pattern

*The urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable, but must have been present previously.)*

In two studies, researchers were able to separate circadian effects from the impact of both recumbence and rest on symptoms of RLS.<sup>(23,24)</sup> Over a 72-hour period, Hening and colleagues evaluated patients with fairly severe RLS for motor restlessness,<sup>(24)</sup> and Trenkwalder and coworkers evaluated a similar group of patients for PLM.<sup>(23)</sup> Both studies included polysomnographic recordings taken after both normal sleep and a day-and-a-half of sleep deprivation. While awake, subjects maintained a relatively constant routine. During modified SIT procedures, they were asked to be still but could allow PLM or motor restlessness to occur when driven by their RLS symptoms. Subjects were monitored polysomnographically for sleep and leg movements throughout the test period. Results of these studies showed a peak in RLS restlessness between the hours immediately after midnight, and a decrease in symptoms in the

late-morning hours (10 am to 11 am). The largest number of PLM occurred on the falling phase of the circadian core-temperature curve, and the smallest number of PLM on the rising phase of the curve.

In patients with advanced RLS, diagnosis may require a retrospective analysis of signs and symptoms. These individuals may have symptoms 24 hours a day without apparent daily variation. Earlier in the course of their disease, however (when their symptoms were milder), these patients typically had symptoms that were worse in the evening or at night. People who experience RLS only with prolonged periods of inactivity and rest, such as on airplane trips, may not be aware of any worsening in the evening or night, although they may report that their symptoms are worse when the prolonged activity occurs in the afternoon or evening than in the morning.

### Supportive Clinical Features of RLS

Although the following features are not essential to a diagnosis of RLS, their presence can help resolve any diagnostic uncertainty.

#### 1. Family history

The prevalence of RLS among first-degree relatives of people with RLS is 3 to 5 times greater than in people without RLS.<sup>(19;22;25;26)</sup>

#### 2. Response to dopaminergic therapy

Nearly all patients with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine-receptor agonist at dosages very low compared with those prescribed in the treatment of Parkinson's disease.<sup>(27-35)</sup> This initial response, however, is not universally maintained.

3. Periodic limb movements (during wakefulness or sleep)

Periodic limb movements in sleep (PLMS) occur in about 80% of people with RLS<sup>(36)</sup>; however, PLMS is also common in conjunction with other disorders and among the elderly.<sup>(37-49)</sup>

#### Associated Features of RLS

1. Natural clinical course following certain identifiable patterns

The clinical course of RLS varies considerably, but certain patterns have been identified. Onset of RLS in patients younger than 50 years tends to be more insidious. When the age of onset is 50 years or older, symptoms often appear more abruptly and more severely.<sup>(17;22;50)</sup> In some patients, RLS can be intermittent and may remit spontaneously for many years.

Clinical experience, derived primarily from more-severe cases of RLS, has until recently contributed to the conclusion that RLS is generally a chronic condition. In patients with milder RLS, however, its pattern of expression appears to be variable, with long periods of remission and sometimes with expression only for a limited period. Among patients whose symptoms start in young adult life and who eventually seek treatment, symptom severity and frequency typically increase over time.<sup>(25)</sup>

Secondary RLS tends to remit without evidence of reoccurrence when the secondary condition is resolved — for example, after renal transplantation in patients with end-stage renal disease,<sup>(51;52)</sup> and postpartum in women with RLS occurring in pregnancy.<sup>(53)</sup> Lee and colleagues studied RLS during pregnancy and reported that one of the seven women

who developed RLS during pregnancy continued to experience symptoms postpartum, suggesting that pregnancy may be a risk factor for the development of RLS. The frequency of RLS during pregnancy (23%) is higher than the frequency (14%) of RLS in women beyond their childbearing years,<sup>(53)</sup> which is itself substantially above the background rate of the population. As will be addressed below, iron deficiency is a possible unifying factor in RLS, and both of these conditions (pregnancy and aging) may tend to create a borderline condition for iron stores.

2. Sleep disturbance

Disturbed sleep is a common major morbidity for RLS and deserves special consideration in planning treatment. Sleep disturbance is often the primary reason the patient seeks medical attention.

In this context, sleep disturbance refers to the subjective experience of disrupted sleep — including reduced sleep time — and not to findings from such objective assessments of sleep as clinical polysomnography. An exception is noted where objective measures clearly reflect the subjective experience, such as shortened sleep duration, sleep efficiency disrupted by awakenings, or increased latency. The diagnostic criteria require that RLS symptoms involve an urge to move and are brought on or exacerbated by rest. Because sleep onset requires a period of rest and because motor activity promotes alertness, the conditions needed to initiate sleep — at the start of sleep time or after an awakening during the night — tend to produce RLS symptoms, and the methods used to relieve the symptoms are likely to interfere with sleep. Thus, RLS

**Table 2 | Representative patient descriptions of RLS sensations in the legs**

- Like an electrical current
- Like Coca Cola bubbling through my veins
- The 'gotta moves'
- Aching in my bones
- Like maggots crawling through my limbs
- 'Elvis' legs
- Creepy crawly
- Throbbing
- Like a toothache in the legs
- The 'heeby-jeebies'
- Crazy legs
- 'Jimmy' legs
- Painful
- Pulling
- Tearing
- Itching bones
- Growing pains

interferes with both initiation and maintenance of sleep. A patient with moderate-to-severe RLS may average less than 5 hours of sleep per night and may be more sleep deprived on a chronic basis than patients with almost any other persistent disorder of sleep,<sup>(54)</sup> and the reduced sleep efficiency correlates with the reported clinical severity of RLS.<sup>(55)</sup> For patients with mild RLS, sleep disturbance may be a less significant issue.

The timing of an individual's RLS depends on both the basic circadian pattern of expression and the conditions under which it is expressed. Onset with rest is variable; patients with milder symptoms tend to have symptom onset after longer periods of rest. Many patients with mild RLS report that their

symptoms bother them only when they must be immobile and stay awake for a significant period of time, particularly in such soporific or movement-restrained situations as airplane flights or an evening at the theater. Others describe mild symptoms at sleep onset, which resolve with small movements or cease when the patient falls asleep. A good sleeper or someone with chronic insufficient sleep may fall asleep rapidly enough that the period of rest before sleep is too short to allow symptoms to develop to a significant degree.

Because sleep problems remain the primary morbidity for most patients seeking treatment, they are considered to be characteristic of the full expression of the disorder, and are clinical features of moderate-to-severe RLS. In light of the frequent occurrence of these disturbances in other disorders, however, and their limited occurrence among patients with milder RLS, they are not considered necessary for or supportive of the diagnosis of RLS.

3. Medical evaluation/physical examination The physical examination is generally normal and does not contribute to the diagnosis except for those conditions that may be comorbid or secondary causes of RLS. Iron status, in particular, needs to be evaluated because decreased iron stores are a significant potential risk factor that can be treated. The presence of peripheral neuropathy and radiculopathy should also be determined because these conditions have a possible, although uncertain, association and may require different treatment.<sup>(22)</sup> Factors that may exacerbate symptoms of RLS (such as end-stage renal disease, pregnancy, and iron deficiency)

may alter the treatment plan or make effective treatment more difficult to establish, and must be ruled out. Aside from the established causes of secondary RLS, no physical abnormalities are known to be associated with RLS. A low-normal serum ferritin level (<45-50 mcg/L) is reportedly related to increased severity of RLS, and — even in patients with normal hemoglobin levels — may be associated with increased risk of the occurrence of RLS.<sup>(56;57)</sup> Measurement of serum ferritin level and percent iron saturation is now considered part of the standard medical evaluation for RLS.

## RLS Pathophysiology

The recent expansion of knowledge about the pathophysiology of RLS can be roughly divided into three areas: 1) *localization of anatomic substrate*; 2) *neurotransmitter systems*; and 3) *iron metabolism*.

### Anatomic Localization of Dysfunction Associated with RLS

A variety of studies have attempted to identify relationships between RLS and peripheral, spinal, subcortical and cortical activity. Considerations of peripheral vs central pathology are based largely on pharmacologic studies. Dopaminergic agents that cross the blood-brain barrier alter RLS, with L-dopa and agonists reducing<sup>(58)</sup> and antagonists exacerbating<sup>(59)</sup> symptoms. In contrast, the dopamine antagonist domperidone, which has limited central action, does not appear to alter RLS symptoms. Thus, in successful treatment trials, a peripheral dopamine antagonist has been used with central dopamine agonists to reduce the peripheral adverse effects without

altering the efficacy of the treatments.<sup>(32)</sup> To the extent that the dopamine treatment involves correction of underlying abnormalities, RLS pathology appears to involve the central nervous system and not the peripheral nervous system.

In the central nervous system, spinal mechanisms appear to be involved in the generation of PLM, particularly periodic leg movements in sleep. Patients with high cord transections commonly have significant PLM,<sup>(42;60;61)</sup> but these are less frequent than those seen in more severe RLS and without the pronounced circadian pattern required for the diagnosis of RLS. Dopaminergic treatment reduces PLM occurring with cord transection by only about 30%<sup>(60)</sup> compared with the 80% to 100% reduction seen for the PLM with RLS.<sup>(62;63)</sup> Thus it seems that spinal pacers could contribute to the observed periodicity of limb movements seen in RLS; independent pacemakers could account for the different periodicities sometimes noted in different limbs of the same patient,<sup>(64;65)</sup> but these alone do not suffice to explain the phenomenology of the PLM observed with RLS.

Reflex studies have in general failed to show abnormalities for RLS patients. Brainstem and transcortical reflexes have not been found to be consistently abnormal.<sup>(66;67)</sup> Blink reflex was reportedly abnormal for sleep apnea patients with PLMS compared with similar patients without PLMS, but a controlled study of RLS patients failed to confirm this finding.<sup>(68)</sup> One exception to these negative reflex studies stands out. The spinal flexor response, measured by stimulation of the medial plantar nerve and bilateral recording from antagonist leg and thigh muscles,

appears enhanced in sleep compared with waking in RLS patients, the reverse of the pattern seen in normal controls.<sup>(69)</sup> These results may suggest that RLS pathology involves increased (rather than the normal decreased) spinal cord excitability that occurs with sleep, but this is likely to result from changes in subcortical regulation of spinal function.

Studies of RLS patients have also failed to find indications for a primary cortical dysfunction; cortical prepotentials were not found to occur with either PLMW or PLMS.<sup>(70)</sup> Transcranial magnetic stimulation studies have found that, compared with controls, RLS patients show reduced intracortical inhibition for both foot and hand,<sup>(71)</sup> and an increased cortical silent period without other changes.<sup>(72)</sup> These findings suggest abnormal subcortical functioning.

One functional MRI study found increased activation in the thalamus and cerebellum associated with RLS sensations without movements and additional increases in activation for RLS sensations associated with PLM. There were no increases in activation of cortical areas.<sup>(73)</sup>

Finally, one study reports results from lesions of the subcortical A11 dopamine system in rats.<sup>(74)</sup> This A11 dopamine system includes the cell bodies for the spinal dopamine neurons that may be modulating nociceptive responses.<sup>(75)</sup> The lesioned rats showed increased startle response and increased locomotion, possibly suggesting the motor restlessness of RLS. It remains unclear, however, to what degree this provides a model for RLS, given the limited behavioral data available on these animals and the uncertain nature of the actual motor changes observed.

Overall, these studies suggest that the primary anatomic substrate with abnormal functioning in RLS likely involves subcortical areas of the brain, with decreased inhibition of the sensorimotor cortical system and (particularly during sleep) the spinal system.

## Neurotransmitter Systems Involved in RLS

### Brain Dopaminergic Function in RLS

Both Akpinar<sup>(10)</sup> and Montplaisir and colleagues<sup>(63)</sup> somewhat serendipitously discovered that low doses of levodopa provide — at least temporarily — almost complete relief from RLS symptoms in some patients. It now appears that all of the dopamine agonists can be used to treat RLS, and the excellent treatment response to very low doses of these medications supports the concept that RLS may involve abnormalities in dopaminergic function. There have also been six PET or SPECT studies with larger-than-minimal sample sizes (sample size larger than 4). A PET study identified a decrease in dopamine-2 receptor (D2R) binding potential in basal ganglia for RLS patients.<sup>(76)</sup> Three SPECT studies, however, produced conflicting results. D2R binding in the basal ganglia for RLS patients (compared with controls) showed no significant difference in one study,<sup>(77)</sup> but showed reduced binding in the other two studies.<sup>(78;79)</sup> This is a confounding variable because of the known decrease in D2R with age.<sup>(80)</sup> In the other studies, however, the subjects and controls were age-matched.<sup>(76)</sup> Two of the SPECT studies<sup>(78;79)</sup> also reported no difference between RLS patients and controls for DAT binding in the

striatum. All of these studies, however, were conducted at a time of day when patients were asymptomatic and therefore it is unclear how the findings relate to the symptomatic state. The changes may reflect a compensatory change in the DA pathway that exists during the asymptomatic period. Moreover, none of these studies measured D2 Bmax, the D2 release or the extracellular dopamine. RLS patients were compared with controls in two PET studies using fluorodopa. Both studies showed significantly less uptake (about 11% to 12% less,  $p < 0.05$ ) for RLS patients in the putamen<sup>(76)</sup> and only one showed a change (10% less uptake in RLS patients) in the caudate.<sup>(79)</sup> Fluorodopa PET studies have been used to define changes in neuronal density in the basal ganglia in Parkinson's disease. However, despite predicted neuronal loss of 80% or greater in Parkinson's disease, fluorodopa studies have not shown consistent positive results. Increases in fluorodopa uptake have been reported in schizophrenia. Fluorodopa is not specific for DA neurons because serotonergic cells also take up this ligand. The exact significance of the fluorodopa changes in RLS is unclear.

Finally, one study using samples of cerebrospinal fluid (CSF) collected from RLS patients in the midmorning found that homovanillic acid (HVA), the primary dopamine metabolite, did not differ significantly from that of controls.<sup>(81)</sup> Both this CSF study and the imaging studies were performed during the daytime when RLS patients are typically not symptomatic. These studies need to be repeated during the evening or night when subjects are symptomatic.

## Opioid vs Dopaminergic System Involvement in RLS

Opiates provide good treatment for RLS, sometimes yielding nearly complete remission of symptoms, although often at relatively high doses.<sup>(82;83)</sup> One study, performed during subjects' normal waking hours, used a suggested immobilization test to compare the effects of standard doses of opiate and dopamine antagonists on the occurrence of PLM.<sup>(52)</sup> In that study, administration of a dopamine antagonist (metoclopramide) increased the number of PLMW, but an opiate antagonist (naloxone) failed to produce a similar consistent change. Thus, involvement of the dopamine system in RLS pathophysiology seems probable, but involvement of the opiate system is less clear.

## Iron Metabolism and RLS

The three major, reversible secondary forms of RLS — pregnancy, end-stage renal disease (ESRD), and iron deficiency anemia — are associated with iron insufficiency. In pregnancy, a woman's body often has difficulty maintaining adequate iron stores, leading to low levels. Other factors, including folate problems, are common in pregnancy and may be related to RLS, but iron seems likely to be the most significant factor, although there have been no studies to date demonstrating this relationship. The critical finding is that all conditions that produce problems with inadequate iron also produce RLS, suggesting that the iron insufficiency may be a significant feature of the pathophysiology of RLS. Several studies support this relationship.

Serum levels of ferritin, the primary storage unit for iron, have been found to correlate inversely with RLS severity.<sup>(56;57)</sup> In one study, CSF levels of ferritin were low and transferrin levels high for RLS patients compared with age-matched normal subjects<sup>(14)</sup>; both changes are those expected to be found with iron insufficiency. Moreover, the values for the RLS patients fell outside the normal range; that is, every RLS patient showed an abnormally low ferritin or a high transferrin or both. One MRI study reported that iron content in the substantia nigra and putamen was significantly lower in RLS patients compared with normal controls, and that the degree of the abnormality related to the severity of RLS symptoms.<sup>(15;81)</sup>

Treatment with iron, either orally<sup>(57)</sup> or intravenously,<sup>(84)</sup> has been found to improve or even completely resolve all RLS symptoms in some patients. Improvement in iron status by intravenous administration of iron and erythropoietin reduces the PLMS in patients with ESRD.<sup>(85)</sup> Orally administered iron supplements can sometimes correct iron deficiency and reduce RLS symptoms.<sup>(57)</sup> Summarizing the results of these studies, it appears that RLS pathophysiology involves the metabolism of iron, particularly in the brain. Moreover, the iron treatment data suggest that iron insufficiency — even if restricted to the brain — may in fact cause RLS.

The putative causal relationship between iron and RLS is further supported by data indicating that iron deficiency disrupts the brain's dopaminergic system. Iron is a necessary cofactor for tyrosine hydroxylase, the rate-limiting enzymatic step in the production of dopamine.

Moreover, iron-deprived rats show reduced brain iron concentrations, which, in the striatum, produce an interesting pattern of decreased D2R,<sup>(86)</sup> decreased dopamine transporter,<sup>(87)</sup> and increased extracellular dopamine.<sup>(88;89)</sup> The decreased D2R and dopamine transporter match the results from the PET and SPECT studies in RLS patients. Thus, iron deficiency produces dopamine abnormalities in animals similar to those seen in RLS patients.

Finally, one recent autopsy study evaluated the brains from seven RLS subjects and five age-matched controls.<sup>(90)</sup> Standard pathologic assessment showed no gross abnormalities in numbers of cells, general cell distribution or morphology. However, histologic evaluation, which was restricted to the substantia nigra, revealed reduced iron, decreased H-ferritin and increased transferrin. All three indices of iron status support the notion of iron deficiency, at least in the substantia nigra. The importance of this brain region is that it contains the cells of one of the major dopaminergic pathways, although it is not known to be involved clinically in RLS. In any case, it seems likely that RLS is a subcortical brain dysfunction involving the dopaminergic system and — at least for some (if not most) patients — regional brain iron insufficiency.

## Disease Course

Idiopathic RLS can begin at any age, even in early childhood, but the condition is increasingly common with age, and some individuals become symptomatic only in their elderly years.<sup>(25;91;92)</sup> Some patients experience remissions in which their symptoms decrease significantly or

disappear for a period of time; usually, however, symptoms continue and often become more severe over time. Patients who develop RLS in association with another medical condition in general will develop symptoms rapidly over a few years. In contrast, patients whose RLS is not related to any other medical condition, and who report symptoms beginning in childhood or young adult life, show a slower progression of symptoms.<sup>(22)</sup>

## Prevalence

It is now clear that symptoms of RLS are commonly reported by European populations, especially those from Western and Northern Europe, as well as populations derived largely from these regions. Typical prevalence for endorsing symptoms in large-scale population studies using questionnaires, including criteria which require some minimum frequency of symptoms, range from approximately 6% to 15% for the entire adult range. While earlier studies used single questions or questions developed by a single group, more-recent studies have attempted to match the criteria for RLS established by the IRLSSG first promulgated in 1995.<sup>(5,6)</sup> In a 1994 Canadian survey, 15% of respondents reported “leg restlessness at bedtime”; 10% reported “unpleasant leg muscle sensations associated with awakening during sleep and with the irresistible need to move or walk.”<sup>(93)</sup> (Table 2)

According to the National Sleep Foundation’s 1998 Omnibus Sleep in America Poll, 25% of adults report experiencing unpleasant feelings in their legs (such as creepy, crawly or tingling sensations) a few nights a month or more; 15% a few nights a

week or more; and 8% every night or almost every night.<sup>(94)</sup> Of those who reported such RLS symptoms, 50% said that the leg pain kept them from getting a good night’s sleep. This survey also found that almost 25% of individuals over age 65 have symptoms of RLS. Three percent of the respondents to this nationwide survey reported that their doctors have told them they have RLS. Polls repeated annually from 1999 through 2002 reported comparable results.<sup>(95-99)</sup>

Included in the 1996 Kentucky Behavioral Risk Factor Surveillance Survey were questions addressing the presence of RLS symptoms; 5.9% of those surveyed reported experiencing RLS symptoms very often, and another 4.1% reported experiencing symptoms often, for a total of 10%.<sup>(100)</sup> In this population-based survey, Phillips and colleagues asked 1803 men and women, via telephone, whether they experienced symptoms of restless legs 5 or more nights per month. They found a clear age-related increase in the prevalence, with 3% of affected participants aged 18 to 29; 10% aged 30 to 79 years; and 19% 80 years and older, with no difference between men and women.

Subsequent studies from Sweden,<sup>(101,102)</sup> Chile,<sup>(103)</sup> and Europe<sup>(104)</sup> have reported similar results, while one study in Switzerland among younger individuals found a 4% prevalence.<sup>(101)</sup> Additional studies on these populations have also been reported in abstract form (through 2003) and all are consistent in finding symptom endorsement in the same 6% to 15% range for a broad spectrum of adult ages. Some studies conducted on clinical populations have found higher frequencies of symptom prevalence.<sup>(105;106)</sup>

Notably, all studies in European populations have reported a higher prevalence of symptoms in women, ranging from a small excess to an almost two-fold difference. Another consistent aspect: an increase in prevalence throughout adult life, lasting through late middle age. Studies are inconsistent as to whether prevalence continues to increase in the elderly (over 65 years old), plateaus, or decreases. Associations that have emerged from population studies include links to psychiatric disorders, general health, and smoking. The Kentucky study found associations to body mass index, lower socioeconomic status, diabetes, lack of exercise, and (seemingly paradoxically) alcohol abstinence.<sup>(100)</sup>

Prevalence figures in non-European populations have been scant, but have suggested there may be lower frequency of RLS in those populations. In Singapore, fewer than 1% of surveyed individuals were found to have symptoms of RLS.<sup>(107)</sup> In Japan, 5% were reported to endorse questions probing RLS,<sup>(108)</sup> but in this population symptoms were more common in men, quite distinct from the European pattern.

A major drawback of almost all of these population studies is that they have not been validated by face-to-face diagnostic interviews, so it is unclear how good an estimate of clinical RLS severity, if any, these studies provide. However, the growing concern about diagnosis, revision of diagnostic features,<sup>(55)</sup> and interest in establishing a more precise estimate of prevalence in different populations suggests that more-reliable studies may be reported in the near future.

A different kind of study has diagnosed patients in face-to-face

**Table 3 | Criteria for the diagnosis of definite RLS in children**

1. *The child meets all four essential adult criteria for RLS, and*
2. *The child relates a description in his or her own words that is consistent with leg discomfort. (The child may use terms such as oowies, tickle, spiders, boo-boos, want to run, and a lot of energy in my legs to describe symptoms. Age-appropriate descriptors are encouraged.)*

or

1. *The child meets all four essential adult criteria for RLS and*
2. *Two of three following supportive criteria are present (see below)*

Supportive criteria for the diagnosis of definite RLS in children

- a) *Sleep disturbance for age*
- b) *A biologic parent or sibling has definite RLS*
- c) *The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep*

interviews. Early studies by Ekbom<sup>(2)</sup> in Sweden and Strang<sup>(109)</sup> in Australia found prevalences of 5% and 3.2%, respectively, in outpatients. A more recent study using face-to-face expert interviews was carried out within the World Health Organization's study for Monitoring Trends and Determinants in Cardiovascular Disease (MONICA-Project). Trained physicians assessed the prevalence of RLS in a population over 65 years of age, based on the four minimal standard criteria, and added several other questionnaires and clinical examinations. Among the 369 participants,

the overall prevalence of RLS was 9.8%, and was higher in women (13.9%) than in men (6.1%).<sup>(110)</sup>

### Genetics of RLS

A strong familial component in RLS has been suspected since Ekbom published his seminal description of the disorder in 1945.<sup>(2)</sup> Clinical surveys of large groups of RLS patients consistently demonstrate a positive family history in 40% to 60% of affected individuals.<sup>(19,22,25)</sup> In cases identified as “familial,” 25% to 40% of first-degree relatives of affected RLS patients were similarly afflicted. Clinical features shared by individuals with familial RLS include symptom onset before age 30; exacerbation during pregnancy; and sensitivity to alcohol.<sup>(19)</sup> The mode of inheritance seems to be autosomal dominant.<sup>(111)</sup> In other words, 50% of an affected individual's first-degree relatives (i.e., parents, siblings, and children) are likely to be affected by RLS. This confirms and extends an earlier study that revealed a high concordance rate for RLS in identical twins,<sup>(112)</sup> despite reports that expression of the full RLS spectrum (e.g., onset of symptoms) can vary between twins and within families.<sup>(112-114)</sup> Many other cases of RLS — best characterized as “sporadic” — typically appear in later life, and cannot be so readily identified as familial. In this subpopulation, therefore, the contributions of genetic factors to RLS are much less clear and are likely complex.

Studies aimed at identifying the gene(s) causing the familial forms of RLS have not yet borne fruit. Nonetheless, preliminary findings are promising, and the hunt for causative genes has been taken up by several groups within four genetically

distinct populations across the world (in Canada, Northern Italy, Germany, and Iceland). A major susceptibility locus for RLS has been reported on a region on the long arm of chromosome 12 in a study of French-Canadians in Quebec.<sup>(115)</sup> The significance of this finding is unclear, however, because linkage could not be confirmed in some kindreds; and results could not be replicated in two large families from South Tyrol.<sup>(116)</sup> The finding of genetic linkage of RLS to a region on the long arm of chromosome 14 in a study of a 30-member, three-generation Italian family represents the first localization of a locus consistent with an autosomal dominant mode of inheritance.<sup>(12)</sup> The region is 14q13-21, which includes — among more than 60 genes — the somatostatin receptor 1 gene (SSTR1) and survival of the motoneuron-interacting protein 1 gene (SIP1).

Of particular relevance in this study was characterization of RLS as a phenotypic spectrum that includes periodic leg movements but lacks subjective appreciation of restless legs, and the fact that two additional large families lacked linkage to either the 12q or 14q loci.<sup>(12)</sup> Thus, RLS appears increasingly to be a complex disorder likely influenced by many genetic factors (rather than a single hereditary component). Given the intensity of research in diverse populations, the future promises to yield additional information about these genes, increasing recognition and improving treatment of RLS.

### RLS in Children

Literature from the mid-1990s suggests that RLS may occur more frequently in children than previously recognized. The younger

the patient, in many cases, the more difficult is the diagnosis. A workshop at the National Institutes of Health in May 2002 yielded some special considerations for pediatric RLS.<sup>(6)</sup> (Table 3) Further, the identification of a consensus on normative values for nightly PLM rates in children and adolescents has not been achieved, but rates from 5 per hour to as low as zero have been suggested.

### Symptoms

As in adults, the symptoms of RLS in children may include leg discomfort, sleep-onset problems and sleep maintenance problems. In some children the RLS discomfort may be misdiagnosed as “growing pains.”<sup>(117-119)</sup> In others, the leg-jerking during sleep (PLMS) may be the key finding in diagnosis, with leg pains absent or very mild.<sup>(120)</sup> The frequent occurrence of PLMS in a child and RLS in family members suggests an association between RLS and PLMS in childhood. Recent research suggests that cognitive, behavioral, and affective difficulties, especially attention problems (attention-deficit hyperactivity disorder) and oppositional behaviors (oppositional defiant disorder), may be more common in these children.<sup>(118;119;121-126)</sup> Further research is needed to delineate the association of these symptoms with RLS and PLMS, and to determine whether sleep disturbance or other factors may mediate the effect.

### Diagnosis

At the NIH 2002 workshop, specific criteria were developed for the diagnosis of RLS and PLMD in childhood.<sup>(6)</sup> Criteria for definite RLS in children are listed in (Table 3).

Workshop participants intentionally made it difficult to arrive at a definite RLS diagnosis in childhood. However, probable and possible RLS categories were also developed to promote research in this area. Over time, a more simplified diagnostic scheme is expected. In all categories, the importance of a family history of RLS and the occurrence of PLMS is acknowledged.

Until recently, reference to childhood RLS and PLMS in the medical literature was infrequent and often incidental.<sup>(125;126)</sup> However, more-recent reports have documented multiple childhood and adolescent cases.<sup>(118;120;122;123;127-134)</sup> Some of these children’s illnesses are diagnosed as attention-deficit hyperactivity disorder, which probably comprises a constellation of different diseases and entities.<sup>(118)</sup> Onset of RLS prior to age 21 was found in about 40% of adults in three retrospective studies.<sup>(17;25;135)</sup> Recognizing that RLS and PLMS are frequent disorders in adults (albeit vastly underdiagnosed), this research suggests that childhood cases may not be rare.

### Treatment

A few case reports and one case series have assessed treatment specifically for children with RLS and/or PLMD. These case reports have indicated individual responses to strict limit-setting to promote a good sleep schedule; restriction of caffeine; iron supplementation; and medications such as clonazepam, carbidopa/levodopa, pergolide, and clonidine.<sup>(118-120;128;133;134;136)</sup> The two small studies suggesting a possible association between childhood RLS, PLMD and iron deficiency (as determined by measurement of serum ferritin levels) raise some important consid-

erations regarding treatment with iron.<sup>(131;133)</sup> Medications such as benzodiazepines, anticonvulsants, alpha-adrenergic agents,<sup>(134)</sup> and opioids have been used extensively in children with disorders other than RLS, as has chronic use of levodopa for dopa-responsive dystonia.<sup>(137)</sup> An open-label trial of dopaminergic medication in the treatment of six children with RLS demonstrated improvement of the children’s RLS and sleep, as well as their scores for attention and impulsivity.<sup>(122)</sup> In general, however, it is probably best to start with behavioral, sleep-schedule, and sleep hygiene interventions before considering pharmacologic treatments for children with RLS.

### Pregnancy

RLS also frequently occurs initially or is exacerbated during pregnancy. Ekbohm’s early finding of an 11.3% prevalence rate during pregnancy has been supported by subsequent reports showing rates from 11% to 33%, with the prevalence of PLMS being almost universal.<sup>(138-140)</sup> Goodman found that 97 of 500 women (19.4%) with singleton pregnancies had RLS.<sup>(141)</sup> In 16 of these cases, the RLS symptoms antedated the pregnancies, and in 5 of these 16, symptoms became much worse during the third trimester but returned to baseline postpartum. In a recent study on the prevalence of hereditary forms of RLS in a population of 300 RLS patients, Winkelmann and colleagues showed that women with familial RLS experienced the first symptom or the worsening of RLS symptoms significantly more often during pregnancy than did women with sporadic forms of RLS.<sup>(19)</sup>

The cause of the increased incidence of RLS during pregnancy has been hypothesized to be related to iron-deficiency anemia, hormonal changes, and vascular congestion. Two studies have demonstrated a relationship between pregnancy-associated RLS and folate deficiency (before conception and during pregnancy),<sup>(53;142)</sup> and one found lower ferritin levels before conception (but not during pregnancy) in women who eventually developed RLS during pregnancy.<sup>(53)</sup>

## End-stage Renal Disease

Since 1966, researchers have recognized that RLS is more common in patients with ESRD than in the general population, and that RLS occurs both before and after the institution of dialysis treatment.<sup>(143)</sup> Formal studies using questionnaires to ascertain prevalence have shown rates of RLS among this patient group to be from 17% to 62%,<sup>(132;144-153)</sup> though due to the variety of abnormal sensory and motor abnormalities seen in ESRD, both false negatives and positives may be common. The reliability of a self-administered questionnaire to diagnose RLS in ESRD patients was low, possibly because of confusion with other causes of leg pain.<sup>(152)</sup> Uremic patients often suffer from more severe PLMS than do patients with idiopathic RLS.<sup>(154)</sup> Various researchers have attempted to find a relationship between the presence of RLS in patients with ESRD and other markers. Positive correlations have been shown between RLS symptoms and increased levels of blood urea nitrogen,<sup>(132)</sup> anemia,<sup>(146)</sup> peripheral neuropathy,<sup>(149)</sup> and decreased levels of intact parathyroid hormone.<sup>(151)</sup> Both RLS and a PLMS

**Table 4 | Differential diagnosis**

*Potential mimics of RLS:*

- Leg cramps
- Peripheral neuropathy
- Varicose veins
- Painful legs and moving toes
- Intermittent claudication
- Positional discomfort
- Neuroleptic-induced akathisia
- Leg pains from arthritis or other disorder
- Fidgets or nervous leg shaking

index greater than 20 have also been found to be significant independent predictors of mortality in this population.<sup>(155)</sup>

## Diagnosis

The diagnosis of RLS in adults is based primarily on interviews with the patient and the patient's bedpartner. The interview should confirm the presence of the four required diagnostic features (Table 1), and should rule out potential mimics of RLS (e.g., diabetic polyneuropathy with nighttime paresthesias, leg cramps, positional discomfort, arthritic pains) (Table 4). Unfortunately, no available laboratory test can confirm the diagnosis; no specific nervous system abnormality has been identified; and, between bouts of RLS, the patient has normal findings on physical examination. Moreover, patients are usually free of symptoms during the day, the time at which a physician typically sees them. The most valuable tool for any clinician in accurately diagnosing RLS is a full understanding of the disorder.

Evaluation of the symptoms associated with RLS should involve a

general medical history and physical examination to rule out possible secondary causes of the syndrome. In particular, physicians should inquire about factors predisposing to iron deficiency, including menorrhagia in premenopausal women, GI blood loss, and frequent blood donation. Blood tests to exclude anemia, decreased iron stores, and diabetes should be performed. If iron supplementation is being considered, tests should include measures of ferritin, percent ferritin saturation, and total iron-binding capacity. With findings or a complaint suggestive of nerve-root damage or neuropathy, the patient should be evaluated for neuropathy and factors contributing to neuropathy, perhaps with electromyography and nerve-conduction studies.

In light of current data, establishing a diagnosis of RLS in childhood is often difficult. Child-specific criteria that take into account the limited language and conceptual skills of a young child have yet to be developed. Often helpful in diagnosing childhood cases is consideration of the autosomal-dominant mode of inheritance of RLS suggested by genetic studies.<sup>(114;125;135;156)</sup> Diagnosis in a biological parent substantially increases the likelihood that the child has RLS, as is true in such other disorders as childhood migraine and dominantly inherited epilepsy syndromes. Another important consideration is the recognition that children can have moderate to severe PLMS without RLS symptoms, even in families where RLS has been identified.<sup>(119)</sup> Polysomnography is an important tool in this situation to confirm PLMS and assess the severity of the sleep disruption.

## Treatment

The goal of any medical therapy, including the treatment of RLS and PLMS, is to achieve the greatest benefit and incur the fewest risks. Sound treatment strategy, therefore, involves weighing the risks and benefits and beginning with the least-risky treatments.

Low-risk therapies involve the implementation of strategies that patients have identified to relieve their symptoms, avoidance of substances that are known or suspected to exacerbate the symptoms of RLS and PLMS, and treatment of symptoms that are caused by underlying disorders. When RLS or PLMS are associated with underlying disorders, treatment of the underlying condition may alleviate the RLS or PLMS or may decrease the dosage of medication that is necessary to relieve the symptoms of RLS or PLMS.

## Nonpharmacologic Therapies

For patients with mild RLS, nonpharmacologic treatments should be tried before prescribing medications that may have unwanted side effects (especially in the geriatric population). Unfortunately, these nonpharmacologic treatments are less likely to be successful in patients with severe RLS. Treatments such as improved nutrition, exercise, and sleep hygiene are often emphasized.<sup>(157)</sup> The best nonpharmacologic treatments probably are those activities that the patient has already identified as being helpful in reducing his or her symptoms of RLS. These treatments include physical activity, particularly involving the limbs (stretching exercises just before bedtime tend to be helpful); very hot or, less commonly, very cold baths or even alternating

hot and cold baths; or any mental activity that is very engrossing for the patient (e.g., video games, computer programming, painting, needlepoint, or active conversation). Many people with RLS report that their symptoms fluctuate with the degree of their physical activity. A mild to moderate degree of exercise tends to suppress symptoms, while the aftermath of either sustained inactivity or bursts of heightened exercise can increase symptoms in some patients. There are many anecdotal reports of temporary improvement of RLS by physical pressure to the legs such as massage, wrapping the legs with bandages, or even using a vibrating device.

Other suggested nonpharmacologic treatments include transcutaneous electrical nerve stimulation,<sup>(158)</sup> conditioning therapy,<sup>(159)</sup> and various procedures to reduce incompetent veins,<sup>(160)</sup> but none of these ancillary treatments have been clearly established to be effective. In particular, the Edinburgh vein study found that most lower-limb symptoms (including RLS) probably have a nonvenous cause, and surgical intervention (i.e., sclerotherapy or “vein stripping”) is unlikely to alleviate the symptoms.<sup>(161)</sup> One group advocates medical therapy for what they call “hypotonic phlebopathy” (a mild form of venous insufficiency), but their clinical description coincides almost perfectly with the symptoms of RLS.<sup>(162)</sup>

## Substances to Avoid

Among the dietary substances and medications that have been reported to increase the symptoms of RLS or PLMS are nicotine, caffeine, alcohol, most antidepressants, antihistamines (including those

usually included in allergy, cold and sinus preparations), most antiemetics, and most antipsychotics.

Smoking and coffee-drinking should be avoided by RLS patients altogether, if possible, but at the very least should be severely restricted near bedtime. Alcohol may initially offer brief reductions in restlessness and appear to promote sleep, but after 30 to 90 minutes, this effect dissipates and may be superceded by rebound worsening of leg restlessness and sleep-disturbance symptoms.

Tricyclic and serotonin reuptake-blocking antidepressants often intensify symptoms of RLS.<sup>(45)</sup> Paradoxically, some patients respond favorably to the use of these same antidepressants. (Theoretically, these positive responses could have resulted from amelioration of a stress-induced RLS component that was in turn caused by sleep-deprivation or anxiety, things for which antidepressants may be useful. However, such etiologic connections to RLS have not yet been convincingly demonstrated.) Bupropion, a dopamine-active antidepressant, may prove to be a useful alternative antidepressant, as a study in five patients with PLMS showed a reduction in leg movements on sustained-release bupropion.<sup>(163)</sup>

H1-antihistamines, in addition to directly causing drowsiness — sometimes profound and long-lasting (up to 48 hours or more) — can exacerbate RLS, often rather severely. This is probably due to an indirect effect on the dopamine receptors. Indeed, the first “neuroleptic”/antipsychotic — phenergan — was originally brought to the market as an antihistamine, suggesting that there may be overlap between these classes of drugs.

**Table 5 | Primary pharmacologic agents for treatment of RLS**

- Dopaminergic agents
  - *Dopamine-receptor agonists*
    - *Ergotamine dopamine agonists*
    - *Nonergotamine dopamine agonists*
  - *Dopamine precursors*
- Opioids
  - *Benzodiazepines*
  - *Nonbenzodiazepine sleeping medications*
  - *Anticonvulsants*

Metoclopramide and some calcium-channel-blocking agents are dopamine antagonists, and in general their use in patients with RLS should be avoided. A recent research project noted that metoclopramide, when used in the afternoon, produced worsening of restlessness for most of the drug-naïve research subjects with RLS.<sup>(59)</sup> In general, antiemetic medications that act on the dopamine system, such as prochlorperazine or chlorpromazine, may markedly exacerbate restlessness.<sup>(164;165)</sup> This interaction can create a problem when a patient with RLS must undergo surgery or must receive nausea-inducing chemotherapy. In the latter case, domperidone, which is not available in the U.S. but can be obtained from its supplier in Canada (Draxis Health, Inc.), may serve as an alternative. This medication provides excellent treatment for nausea and, because it does not cross the blood-brain barrier, does not affect RLS symptoms. Two newer anti-nausea and anti-emetic medications, granisetron hydrochloride and ondansetron hydrochloride, are selective 5-HT<sub>3</sub> receptor antagonists

with little or no affinity for other receptors, including dopamine receptors.<sup>(166)</sup> Early reports on these drugs are encouraging. They are expensive at present, but as more-widespread experience leads to increased use, prices may go down.

Even the newer types of neuroleptics have been reported to cause *de novo* leg and sleep symptoms that are suggestive of RLS.<sup>(44;167)</sup> In addition, there have been reports of severe exacerbations of RLS after intravenous droperidol anesthesia,<sup>(168)</sup> or oral haloperidol antipsychotic treatment. Some patients develop elevated body temperature and muscle rigidity, a condition that resembles the neuroleptic-malignant syndrome (NMS), but whether these are sporadic cases of true NMS or just a milder clinical mimic is unclear.

### Pharmacologic Treatments

Pharmacologic treatments include primary and secondary therapies. Primary treatments are defined as those that have been established through well-controlled studies to ameliorate the principal sensory and motor features in most RLS patients, with results consistent between diverse study sites. Secondary treatments are those whose efficacy is less well-established and whose reversal of the principal features of RLS is less universal when compared with primary treatments. Because no manufacturers have received FDA approval in the U.S. for the use of their drugs in the treatment of RLS or PLMS, the following recommendations are based either on the results of clinical studies that have been published in peer-reviewed journals or recent large-scale clinical studies presented at a major profes-

sional meeting and abstracted in a major journal. Restex (carbidopa/benserazide) has been approved in Germany and Switzerland for the treatment of RLS.

Pharmacotherapy of RLS should be governed by sound treatment strategies. First, medications should be used at the lowest effective dose, and (in most cases) the dosage should be titrated slowly upward. Second, when a medication is beneficial to a patient and the drug causes no adverse effects, doses higher than the recommended range can be used as long as there is careful monitoring. This strategy is particularly useful in converting a partial alleviation of symptoms to a symptom-free state. Third, medications may need to be administered in divided doses, most commonly with the evening meal and later in the evening. Fourth, because medications may vary in benefits and side effects, the use of a combination of medications may achieve a better outcome than can be realized with the use of a single medication. The lowest effective dosage of each component of the combination should be used. The best treatment is often arrived at empirically — that is, only by experimentation with a variety of agents. Active communication between the physician and patient is imperative, with the physician resisting the temptation to forgo an established treatment option until a maximal tolerable dose is realized.

### Primary Treatments

Primary pharmacologic treatments are principally aimed at two classes of medications: dopaminergic agents and opioids (Table 5). Both classes have been

consistently demonstrated to reverse not only the subjective features, but also the objective features (PLMS and associated sleep architecture abnormalities) of RLS. Because of the tolerance and dependence associated with the use of opioids, dopaminergic agents remain the mainstay of first-line treatment. Benzodiazepines and anticonvulsants, while included as primary pharmacologic treatments, exhibit varying degrees of effectiveness. One anticonvulsant, gabapentin, has been evaluated in a reasonably large, well-designed, recent clinical trial.

### Dopaminergic Agents

Dopaminergic agents that increase the level of available synaptic or postsynaptic dopamine are classified as dopamine precursors, acting upon dopamine receptors (e.g., dopamine-receptor agonists), are increasingly recognized as the mainstay of primary pharmacologic therapy. Well-controlled clinical trials at a number of centers have established their efficacy in reversing both RLS and PLMS. They improve not only subjective discomfort, but also PLMW, PLMS, and sleep quality.

### Dopamine Precursors

Dopamine precursors, either regular carbidopa/levodopa or carbidopa/benserazide or sustained-release carbidopa/levodopa act by delivering levodopa to the brain, where it is converted to dopamine. The carbidopa component acts to retard the peripheral breakdown of levodopa, increasing the availability of levodopa to the brain. Typical doses are in the range of 25/100 to 100/400 (mg carbidopa/mg levodopa) taken in divid-

ed doses before bedtime and during the sleep period.<sup>(169-171)</sup> Side effects include gastrointestinal discomfort, nausea and vomiting, and headache. The degree to which sustained-release preparations overcome this problem is not clear. Long-term treatment of RLS does not typically lead to the kinds of abnormal movements that follow treatment of Parkinson's disease with carbidopa/levodopa (e.g., dyskinesias). A recent randomized, double-blind, placebo-controlled multicenter crossover trial of 32 patients by Benes et al. in Germany has further established the efficacy of levodopa in combination with an agent to prevent its peripheral metabolism.<sup>(27)</sup> Most remarkable was the near-immediate onset of action realized with levodopa, which lends support to those advocating short trials of levodopa for patients in whom the diagnosis of RLS is in doubt. Review of the literature also advocates for the use of levodopa/carbidopa in the management of RLS in the hemodialysis population.<sup>(172;173)</sup> Two significant and common problems with the use of carbidopa/levodopa have been noted: 1) the short half-life of the drug, compounded by the tendency of symptoms to recur later in the night after initial response to treatment, often leading to poor sleep quality; and 2) the development of rebound<sup>(174)</sup> and augmentation.<sup>(175)</sup> Rebound is the tendency of symptoms to worsen at the end of a dosing period, leading to late-night or morning recurrence of symptoms and PLMS. It is most common with the use of short-acting preparations such as regular release of levodopa/carbidopa. Augmentation is the tendency for symptoms to develop

earlier in the day (e.g., morning or late after-noon instead of mid-evening) and to be more severe than the symptoms that occurred before treatment with carbidopa/levodopa began. Most recent experience suggests that augmentation can be a complicating feature in 65% to 80% of cases. The exact mechanisms contributing to augmentation are not known, but — empirically — doses of levodopa in excess of 200 mg per day are frequently associated with this phenomenon. Moreover, it is more common in severe forms of RLS than in mild cases. The temptation to increase the dosage of levodopa to overcome augmentation should be avoided because increasing the drug further exacerbates the problem. Augmentation is the most serious and common complication associated with carbidopa/levodopa therapy. All RLS patients who take this medication should be carefully monitored for development of augmentation. The best treatment option is to change to dopamine-agonist therapy. Most cases of augmentation respond in a matter of days or weeks to the withdrawal of levodopa, which should be done prior to initiating dopamine-agonist therapy.

### Dopamine-receptor Agonists

Dopamine agonists act via activation of central dopamine D2 receptors, which are located pre- and postsynaptically. Increasingly they are being used as first-line agents for RLS, because of their efficacy in alleviating the subjective and objective features of RLS, their tendency to be well tolerated, and the apparent lower rate of complications such as rebound and augmentation as compared with levodopa treatment.

Augmentation is the tendency for symptoms to develop earlier in the day and to be more severe than the symptoms that occurred before treatment began; rebound is the tendency of symptoms to worsen at the end of a dosing period, leading to late-night or morning recurrence of symptoms and PLMS.

### Ergotamine Dopamine Agonists

#### *Pergolide*

Several open-label<sup>(176-178)</sup> and randomized, double-blind, placebo-controlled trials<sup>(30-32)</sup> have shown efficacy with pergolide in the treatment of RLS. In an open-label trial, Earley and Allen found that pergolide has the same efficacy and fewer side effects than carbidopa/levodopa, with pergolide resulting in only minimal augmentation.<sup>(30)</sup> Silber et al. showed good therapeutic effects with the use of pergolide in patients for whom levodopa treatment was not efficacious or had created unacceptable augmentation effects; however, these researchers noted fairly frequent side effects, such as nausea and nasal congestion and somewhat common augmentation.<sup>(177)</sup> Winkelmann and colleagues treated 15 patients (13 idiopathic, 2 secondary) who had developed augmentation on levodopa therapy with pergolide starting at 0.05 mg (2 hours before bedtime).<sup>(179)</sup> After 3 to 5 days of treatment, the daytime augmentation disappeared, and all patients reported a dramatic reduction of symptoms. After 6 months, 14 patients remained on a minimal dose of 0.1 mg per day.

In a double-blind, randomized, crossover study of pergolide vs levodopa, Staedt and colleagues found that 9 of 11 patients had a “complete relief of restlessness” and the remain-

ing 2 patients had a “nearly complete relief” on pergolide, with only one patient in the levodopa group achieving “complete relief of nighttime restlessness.”<sup>(31)</sup> Nine patients on pergolide experienced severe nausea, which was successfully treated with domperidone (not available in the U.S.). Earley and Allen, in a randomized, double-blind, placebo-controlled study found that pergolide significantly improved symptoms of RLS, including dysesthesias in eight subjects.<sup>(30)</sup> None of the modest side effects required discontinuation of the medication. In this study, the researchers used a divided evening dosage schedule, with approximately equal doses given with the evening meal and again 1 hour before bedtime. Pieta et al. used up to 0.25 mg of pergolide at bedtime to treat RLS symptoms in eight patients with ESRD; five patients reported a subjective improvement in RLS symptoms and sleep quality, but polysomnographic results showed only slight improvements.<sup>(180)</sup> Wetter et al. used a protocol similar to that of Winkelmann et al. (domperidone 3 times a day in conjunction with a 2-hour-before-bedtime, single dose of pergolide) in 30 patients with idiopathic RLS who had remained psychotropic-drug free for 2 weeks before and during enrollment in the study.<sup>(32)</sup> Pergolide, at a mean dose of 0.5 mg/d, was superior to placebo in reducing the number of PLMS; increasing the total sleep time; and improving subjective sleep quality, quality of life, and severity of RLS. Stiasny and colleagues reported a 1-year open-label follow-up from this study showing that 22 of 28 of the patients (78.6%) continued on pergolide and 6 patients discontinued it.

Mean pergolide dose was 0.37 mg per day. Six patients developed augmentation during the year of follow-up.<sup>(181)</sup> The design of a double-blind placebo-controlled study of 100 patients involving 17 centers mostly in Europe using polysomnographic evaluation has been described.<sup>(182)</sup> This represents the first large-scale study of any medication in the treatment of RLS.

In summary, pergolide — given either as a single dose before bedtime or in divided doses in the late afternoon or evening and 1 hour before bedtime — provides well-established and effective treatment for the sensorimotor symptoms of RLS and associated sleep disturbances. The initial dose of pergolide is typically 0.05 mg and is carefully titrated upward to avoid symptomatic hypotension. Nausea, constipation, and hypotension are potential side effects, and can be alleviated with coadministration of domperidone (not available in the U.S.).

### Non-ergotamine Dopamine Agonists

The newer dopamine agonists appear to be as beneficial as pergolide and, because they are not ergot-derived, may be associated with fewer side effects. These are listed below in alphabetical order.

#### *Pramipexole*

Two open-label trials and one double-blind, randomized, crossover trial of pramipexole in the treatment of RLS have recently been published.<sup>(183-185)</sup> Lin et al. treated 16 patients without adverse events.<sup>(183)</sup> One patient dropped out of this open clinical trial due to insomnia. RLS was effectively treated at an average dose of 0.3 mg per day. Becker and

colleagues conducted a multicenter, 3-month study that included 23 patients who had received a variety of previous treatments for RLS.<sup>(184)</sup> Nineteen patients reported significant improvement and remained on pramipexole therapy after the study period, with 17 reporting that this was their preferred treatment for RLS symptoms. None of the patients developed augmentation, and adverse events of sleepiness and dyspepsia were mild. Montplaisir et al. studied 10 RLS patients in a 1-month double-blind, placebo-controlled crossover fashion.<sup>(33)</sup> Leg discomfort was alleviated at bedtime and during the night, both objectively and subjectively. Most remarkable was the near-absolute resolution of PLMS — to levels considered normal — with pramipexole. The authors recommended a total daily dosage between 0.375 mg and 0.75 mg, as little therapeutic gain was realized by increasing the dose to 1.5 mg, and this increase possibly contributed to development of daytime fatigue. Longer-term follow-up of 7 patients demonstrated the safety and long-term efficacy of pramipexole.<sup>(186)</sup>

In summary, pramipexole given as a single dose provides effective, well-tolerated treatment for the sensorimotor symptoms of RLS and associated sleep disturbances. The initial dose is typically 0.125 mg and is carefully titrated upward to avoid common side effects such as nausea and orthostatic hypotension. Patients typically habituate to these side effects in a matter of 7 to 10 days, similar to the pattern established in patients with Parkinson's disease. Other side effects include fatigue or sleepiness, a phenomenon that appears to be dose-related and possi-

bly due to the long half-life of the drug (>10 hours). Dyspepsia, headache, fluid retention, and insomnia have also been reported. Augmentation and rebound have been observed in some patients. Two recent long-term naturalistic studies demonstrate augmentation in roughly one-third of patients taking pramipexole for an average of 2 years.<sup>(187;188)</sup>

### *Ropinirole*

Ropinirole, like pramipexole, is a nonergotamine dopamine agonist. Its efficacy in treating RLS has been less well-established, both in peer-reviewed articles for open-label trials and in recently completed larger scale double-blinded studies that have been presented at major professional meetings and published in abstract form. In light of clinical experience and its pharmacologic likeness to pramipexole, however, this drug is expected to be effective in alleviating RLS. Ondo reported the results of an open-label study of the efficacy and side-effect profile of ropinirole in the treatment of RLS.<sup>(189)</sup> The 16 patients had used an average of 4.2 medications for their RLS, with 8 discontinuing all concurrent RLS medications and 2 reducing their use of other pharmacotherapies. Thirteen patients completed the trial, with 10 reporting that ropinirole was the best overall treatment for their RLS symptoms; 3 discontinued treatment with ropinirole because of side effects (rash and edema, anxiety and tremor, and nausea). Other mild adverse events included sedation or fatigue, nausea, dyspepsia, shoulder pain, acne, and hypomania. Ropinirole therapy was initiated at 0.25 mg per dose (either at bedtime or twice a day, depending on

whether symptoms were in the evening only or day and evening, respectively); doses ranged from 0.5 mg to 12.0 mg, with a mean daily dose of 2.8 mg ± 2.3 mg. Subjective and objective demonstration of alleviation of RLS, associated PLMS, and sleep architecture disturbances have recently been reported following a single 0.5-mg dose of ropinirole in a parallel-group design with active drug and placebo (12 controls vs 12 previously untreated RLS patients).<sup>(190;191)</sup> In two small open trials, Estivill and de la Fuente found ropinirole to improve not only subjective RLS symptoms in 15 patients, but also objective criteria on polysomnography in 5 patients.<sup>(192;193)</sup> Mean total sleep times increased, sleep efficiencies improved, and total number of periodic movements decreased.

Results from two very large clinical trials involving standard double-blind placebo-controlled evaluations over a 12-week treatment period were recently presented at professional meetings and published in abstract form. Ropinirole was evaluated in comparison with placebo. One trial carried out in six countries involved 267 subjects and 47 centers,<sup>(194)</sup> and the other evaluated 243 subjects from 43 centers in 10 countries.<sup>(195)</sup> These two very similar studies represent the largest clinical trials for RLS to date. Both used the IRLS (a validated rating scale developed by the International Restless Legs Syndrome Study Group) and a clinical global improvement (CGI) scale to measure primary outcomes. Both studies used a single dose at or near bedtime. The ropinirole doses started at 0.25 mg, increased gradually over 7 weeks to a maximum of 4.0 mg, and

held stable for the remainder of the study. In both studies, the mean effective dose was 1.9 mg. A fairly large placebo response was reported, a phenomenon also noted in the only previous large-scale clinical study of RLS reported in the literature.<sup>(196)</sup> Both the IRLS and CGI showed clear improvement with ropinirole treatment, statistically superior to the placebo response. Eight percent of subjects taking ropinirole withdrew due to adverse effects — most commonly nausea and headache — compared with 5% of those on placebo. A modestly large (55 patients) double-blind, placebo-controlled, polysomnogram (PSG) study on ropinirole treatment has also been reported at a professional meeting and published in abstract form.<sup>(197)</sup>

In summary, recent well controlled studies have shown ropinirole, given as single dose, to be an effective treatment for the sensorimotor symptoms of RLS, and a modestly large study has shown ropinirole to reduce the associated sleep disturbances. The initial dose is typically 0.25 mg before bedtime, and is carefully titrated upward to avoid common side effects such as nausea and orthostatic hypotension. Divided doses with half of the night dose typically given with the evening meal and the other half at bedtime have been used in open-label studies. The average patient responds to a total dose in the 1.5 mg to 2.5 mg range. Patients typically habituate to side effects in a matter of 7 to 10 days. Other side effects include fatigue or sleepiness. Long-term efficacy and the degree of augmentation of ropinirole have not been established.

## Opioids

Opioid medications, also known as narcotics, have long been known to successfully treat restless legs syndrome. In fact, the use of opioids for RLS symptoms was first described by Willis in the 17th century.<sup>(1)</sup> More recently, there has been some scientific confirmation in controlled trials. Walters et al. evaluated oxycodone (mean dose of 15.9 mg) vs placebo in an 11-patient, crossover trial with 2-week treatment arms.<sup>(82)</sup> They reported a statistically significant improvement in leg sensations, motor restlessness, polysomnographic PLMS and PLMS arousals. Kaplan et al. compared propoxyphene (100 mg and 200 mg doses) to levodopa and placebo in six patients with PLMS in a crossover trial with 10-day treatment arms.<sup>(62)</sup> The 200 mg dose resulted in improved sleep parameters and decreased PLMS arousals, but did not significantly reduce total PLMS or subjective scores when compared with placebo. Most of these medications, however, have been studied less stringently.<sup>(198-200)</sup> Meperidine and propoxyphene may compare negatively with other opiates<sup>(200)</sup>; there have, however, been no formal comparisons among the different medications. Therefore, the selection of any individual opioid is based largely on physician preference. Available opioids are listed below by relative strength: M = mild, I = intermediate, and P = potent. These include codeine (M), pentazocine (M), propoxyphene (M); hydrocodone (I); fentanyl (P), hydro-morphone (P), methadone (P), oxycodone (P); and morphine. Opioids given intrathecally via infusion pump have also been reported to improve RLS.<sup>(200)</sup> This offers several potential

advantages but does require surgical placement of a pump, and thus will likely be reserved for only the most severe cases.

The mechanism by which opioids improve RLS is not clear. It is assumed that they stimulate opioid receptors, similar to their mechanism of action for pain in general. There is, however, some evidence to suggest that they actually work indirectly through dopaminergic mechanisms. In a study of a single case, preadministration of a dopamine antagonist blocked the beneficial effect of a narcotic, whereas preadministration of an opioid antagonist did not reduce the efficacy of a dopaminergic treatment.<sup>(169;201)</sup>

Narcotic medications are usually well tolerated, and demonstrate good long-term efficacy, relatively low addiction potential, and little tolerance in the RLS population.<sup>(83)</sup> Side effects include nausea, sedation, dizziness, and constipation. There are still concerns about abuse potential, addiction, and practical problems arising from the use of “controlled” drugs. Many physicians are not comfortable using narcotic medications to treat a long-term condition. Nevertheless, opioids often provide significant relief for RLS when other treatments have failed, and may also represent the optimum treatment for some patients. Patients can be reassured that taking one nightly dose of an opioid has much less risk of addiction than regular opioid use for acute or chronic pain.

## Benzodiazepines and Other Sleeping Pills

Benzodiazepine medications are useful in the treatment of nocturnal symptoms of both RLS and PLMD, presumably by improving the quality

of sleep. They may also ameliorate the waking symptoms of RLS, but this finding is less well established, and the use of these drugs in the daytime is limited by risks of sedation. The number of PLMS does not always decrease significantly with the use of benzodiazepines, but some studies have shown statistically significant decreases of uncertain clinical significance.<sup>(202)</sup> In an acute placebo-controlled sleep laboratory study of 10 RLS and 16 PLMD patients, 1 mg of clonazepam exhibited acute therapeutic efficacy in both PLMD and RLS with regard to insomnia — quite different from the mode of action of dopamine agonists.<sup>(203)</sup> Clonazepam, in dosages of 0.5 mg to 4 mg; temazepam, in doses of 15 mg to 30 mg; and triazolam, in dosages of 0.125 mg to 0.5 mg are typical bedtime doses.

With both benzodiazepines and opioids, careful patient selection and follow-up for side effects are necessary. Comprehensive reviews of the benzodiazepine literature conclude that inappropriate use, psychological dependence, and physiologic tolerance are distinctly uncommon during the prescribed administration of these agents.<sup>(202; 204)</sup> In a long-term sleep disruptive study of 170 adults, including 136 patients receiving clonazepam nightly for a mean of 3.5 years, only 8% had adverse effects requiring medication changes; 2% had relapses of alcohol or chemical abuse requiring hospitalization; and 2% at times misused their medications. This low risk for adverse effects, dosage escalation or abuse applied also to elderly patients, as well as younger adults. During this study, benzodiazepine withdrawal symptoms typically did not develop

at the time of attempted or successful dose reduction, or upon drug discontinuation.

The newer non-benzodiazepine sleeping pills, such as zolpidem 5 mg to 10 mg and zaleplon 10 mg to 20 mg, may help nocturnal RLS symptoms. Zolpidem has been found to be effective for RLS in one uncontrolled study involving a small population of middle and late onset patients.<sup>(205)</sup>

Caution should be observed in using benzodiazepines with longer half-lives (such as clonazepam), as daytime sedation/decreased alertness may occur (especially in older individuals who may not even recognize this problem), so a shorter-acting sleeping pill like triazolam may be a better choice. Other concerns include the risk of falling at night on the way to the bathroom; also, dependency can occur with all benzodiazepines. Furthermore, benzodiazepine withdrawal may be associated with great discomfort and even seizures.

Newer nonbenzodiazepine sleeping pills such as zolpidem at 5 mg to 10 mg and zaleplon at 10 mg to 20 mg may have some advantages over the older benzodiazepines, including a reduced likelihood of addiction, daytime sedation or withdrawal symptoms. Zolpidem has been found to be effective for RLS in one uncontrolled study involving a small population of middle- and late-onset patients.<sup>(206)</sup>

#### Anticonvulsants

Among the most promising new anticonvulsants for RLS treatment is gabapentin.<sup>(207;208)</sup> In one modest-sized (24 patients) double-blind placebo-controlled crossover study

with 2 weeks for each treatment arm and 1 week washout between treatments, gabapentin significantly reduced the subjective sensorimotor symptoms of both RLS and PLMS during sleep.<sup>(209)</sup> Divided daily doses were used, and the mean effective daily dose was 1,855 mg. The patients in this study had mild to moderate RLS. The medication was well tolerated, and few adverse effects were reported. Subjects who complained of pain as a symptom derived the greatest benefit from gabapentin. Overall, taken in doses of up to 2700 mg per day, gabapentin seems especially useful for treating mild to moderate RLS, particularly in patients reporting pain with their RLS. Large trials have not been carried out, nor has the long-term efficacy of gabapentin treatment been established. Carbamazepine treatment for RLS has been evaluated in a large double-blind placebo-controlled clinical trial involving 174 patients treated over a 5-week period. It was effective in reducing subjective symptoms of RLS.<sup>(196)</sup> Thus it has been suggested that this medication fails to resolve the full spectrum of elements of the RLS disorder. The modest degree of improvement failed to match the dramatic improvement in PLMS reported for the dopaminergic medications, and the adverse effects have led to limited acceptance of this medication in treating RLS. Valproate has also been reported to provide some benefit for RLS, but its acceptance has been minimal, perhaps due to its widely reported tendency to cause weight gain.<sup>(210;211)</sup>

## Secondary Treatment

Secondary treatment is that which has not been as well established or whose efficacy is limited. Bromocriptine has undergone limited study in the treatment of RLS and PLMS, and results are mixed. Walters et al. reported excellent results with the use of bromocriptine,<sup>(30)</sup> but other groups have been less impressed with its efficacy.<sup>(52)</sup> Typical doses for therapy are 5 mg to 15 mg, and side effects are similar to those associated with the use of pergolide. Two other dopamine-receptor agonists, apomorphine and cabergoline, were beneficial in very small studies, with apomorphine (not currently available in the U.S.) being given as an infusion,<sup>(83)</sup> and cabergoline given orally.<sup>(212;213)</sup> Cabergoline has the longest half-life of any dopamine agonist but is approved in the U.S. only for hyperprolactinemia treatment and is prohibitively expensive.

Three studies, two in nonuremic and one in uremic patients, showed that the antihypertensive agent clonidine, a centrally active alpha-adrenergic blocker, diminishes patients' subjective RLS complaints and improves their ability to fall asleep.<sup>(134;205;214)</sup> Baclofen was found in a double-blind study to reduce arousals related to PLMS, primarily by decreasing the response to movements.<sup>(215)</sup> The use of this drug appeared to decrease the intensity of movements, but not their frequency. Its effect on the waking symptoms of patients with RLS is not clear.

An open-label trial of tramadol, a narcotic with a nonopioid mechanism of action, at a dose of 50 mg to 100 mg per day, was very beneficial

in 7 of 12 patients treated for 15 to 26 months.<sup>(213)</sup> Another open-label study found that amantadine, 100 mg to 300 mg per day, benefited 11 of the 21 patients who were treated.<sup>(216)</sup> The mechanism of action for amantadine is unclear but may relate to its glutamate-antagonist properties.

Other medications that have been reported to be effective, sometimes only by singular anecdotes, include beta-adrenergic blockers, serotonin precursors, nonbenzodiazepine sedatives, antidepressants, and vasodilators.<sup>(217)</sup> Paradoxically, many of these same medications may exacerbate RLS symptoms, and the use of these medications cannot be recommended with any confidence. They could be considered for use by patients who have been otherwise unable to tolerate more-established agents or have not responded to them; however, the patient needs to understand that the evidence for benefit is minimal.

## Treatment in Special Populations

### End-stage Renal Disease

Treatment modalities that have been shown to be effective for patients with ESRD and RLS include the intravenous administration of epoetin alfa<sup>(85)</sup> and the use of clonidine<sup>(218)</sup> and dopaminergic agents.<sup>(219-221)</sup> In a recent analysis by Janzen and colleagues of published studies on the use of levodopa in dialysis patients, the authors reported that carbidopa/levodopa was safe and effective in managing RLS in this population, but cautioned that the dosage must be individually titrated and that rebound and augmentation should be monitored. The type of dialysis does not appear to affect RLS.<sup>(172)</sup>

Published case reports and anecdotal evidence show that renal transplantation relieves the RLS associated with ESRD.<sup>(52)</sup>

Use of opioids and benzodiazepines for the treatment of RLS has not been studied in this population. Because of their renal clearance, opioids should be used in smaller-than-normal amounts. Gabapentin should also be used with caution, as it is renally excreted.<sup>(222)</sup>

### Pregnancy

Unfortunately, no drug currently used to treat RLS or PLMS is considered by the FDA to be completely safe (category A).<sup>(223)</sup> Some drugs, including oxycodone, methadone, and pergolide, are classified by the FDA as category B but should be used with only the greatest caution. Other drugs with higher risk (FDA category C) include levodopa, pramipexole, clonazepam, propoxyphene, and gabapentin. Opioids and benzodiazepines can cause neonatal respiratory distress, so they should be discontinued at term, and neonates should be monitored for withdrawal symptoms. Iron deficiency and anemia should be ruled out, and serum ferritin levels should be maintained above 45-50 mcg/L, if possible, during pregnancy. If a diagnosis of RLS is made during pregnancy, the patient should be reassured that symptoms often subside or resolve following childbirth.

### Deficiency States

Correction of deficiency states has often been reported to decrease RLS symptoms. With the exception of the body of work regarding iron deficiency, most of the reports are based

on unblinded evaluations that could be reporting essentially placebo effects. In 1977, Botez et al. suggested a link between RLS and folate deficiency, and found that treatment improved the symptoms of RLS.<sup>(224)</sup> Supplementation with vitamins such as C, E,<sup>(225)</sup> or B12 is more speculatively linked to a deficiency, but no controlled trials demonstrate that these therapies are effective. Two studies have shown a correlation between magnesium deficiency and the presence of RLS symptoms.<sup>(226;227)</sup> Hornyak et al., in their open-label trial, showed improvement in both subjective and objective measures of sleep with magnesium supplementation.

Nordlander demonstrated that intravenous iron therapy brought about a significant resolution of RLS symptoms in well over 90% of subjects treated.<sup>(84)</sup> Unfortunately, this open-label trial used subjective, not objective, measures of patients' symptom severity. The usual serum and CSF iron-related proteins that are currently measured were not assessed in the 1950s when this study was conducted. The oral administration of iron would appear at first to be the simplest and safest way to increase body iron stores. In RLS patients with iron deficiency, use of oral iron supplements will usually bring about improvements in symptoms.<sup>(7)</sup> In RLS patients with normal iron status (as determined by serum ferritin), use of oral iron therapy had decreasing benefit in inverse proportion to the baseline serum ferritin levels: the higher the ferritin at the time of initiating therapy, the less pronounced the benefits. The only randomized, double-blind placebo-controlled trial of iron supplementa-

tion in treating RLS failed to find any significant difference in symptom improvement with treatment.<sup>(228)</sup> However, the patients had higher levels of ferritin than those in O'Keeffe's study, and no clinically significant improvements in the level of ferritin were seen after treatment. This underscores an important biological issue: patients with normal ferritins will absorb very little of the orally delivered iron. The problem in using oral iron to raise body iron stores is that the gastrointestinal tract controls the degree of absorption.<sup>(229)</sup> Under severe iron deficiency states (ferritin <5 mcg/L), the gastrointestinal tract will allow as much as 40% of the oral iron to be absorbed, but with ferritin >60 to 80 mcg/L, probably less than 2% of the non-heme iron is absorbed.<sup>(230)</sup> Therefore, to increase body stores of iron when stores are normal, unacceptably high oral doses would be required for months.

The lower the iron level and the more acute the onset of symptoms, the more likely it is that improvement can be expected in RLS symptoms with iron supplements. The value of raising ferritin levels much above 50 mcg/L remains unclear.

One important caveat in implementing therapy with iron supplementation is to note the nonexclusive relationship between RLS symptoms and the common genetic disease hemochromatosis.<sup>(231)</sup> Excessive iron accumulation in the liver and other organs is seen in hemochromatosis, which has gene prevalence of about 1 in 200. Anyone whose serum percent transferrin saturation is greater than 50 is very likely to have this genetic disorder, even if the ferritin level is in the normal range.

The physician should proceed with caution under these conditions if and when using oral iron supplementation.

With the institution of oral iron supplementation, serum ferritin levels and percent transferrin saturation should be checked at intervals not longer than every 3 months. Supplemental iron may be discontinued once the patient's serum ferritin level reaches 50 mcg/L.

Various iron formulations are available, the most basic of which is ferrous sulfate 325 mg, which contains 65 mg of elemental iron. Ferrous sulfate should be given in combination with 200 mg of vitamin C, which will improve absorption of iron. The combination of iron plus vitamin C should be given about an hour before meals or 2 hours after meals. It should not be given with food.

The value of using intravenously administered iron to bypass the gastrointestinal tract's barrier to iron absorption has yet to be fully evaluated for its long-term safety. Iron can be intravenously administered to a patient with severe iron deficiency who requires immediate access to iron, such as a pregnant woman for whom oral supplementation will not adequately restore iron stores quickly enough. Also, intravenously administered iron is used in many patients who are on dialysis. Use of intravenously administered iron to increase total body iron stores in RLS patients is at best experimental and its use for RLS should not be considered appropriate outside of research protocols.

## Summary

Given the results of recent surveys, it is evident that RLS affects a significant proportion of the general population to some degree. Although lack of recognition has impeded patients' efforts to procure appropriate medical treatment in the past, that need not be the case today. As Ekblom said, "the diagnosis is generally easy if one is familiar with the syndrome," and it is therefore incumbent upon clinicians to familiarize themselves with the symptoms of this common disorder to assist their patients in finding suitable therapeutic interventions.<sup>(2)</sup> However, clinician and patient knowledge of RLS symptoms alone will not lead to diagnosis and treatment. Primary care physicians must include a question about RLS symptoms and sleep disorders in all new-patient and annual physical surveys. Similarly, patients must make their RLS symptoms a top priority in discussion with their physicians. With the armamentarium of medications currently available for the treatment of RLS, patients — working in close cooperation with their physicians — can, in all likelihood, find effective relief from the "place of greatest torture."<sup>(1)</sup>

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## RLS Foundation Research Grants

In pursuit of its goals of identifying effective treatments and finding a cure for RLS, the RLS Foundation has developed competitive-grants and fellowship programs. The Foundation encourages grant applications for basic and clinical research studies into the prevalence, pathophysiology, genetics, and phenotypic definition of RLS and for support of promising predoctoral and postdoctoral candidates. For more information, please contact:

CHAIR, SCIENTIFIC ADVISORY BOARD  
*RLS Foundation*  
 819 Second Street SW  
 Rochester MN 55902-2985

### Application Process

Initial contact should be through a letter of intent, containing the following: a one-page abstract of the proposed project, including its clearly stated relevance in addressing one or both of the RLS Foundation's goals of finding a cure and developing effective treatments; a copy of the principal investigator's NIH-style biobibliography; and a tentative budget as well as a list of other sources of funding.

Basic science leading to a better understanding of RLS, innovative approaches, interdisciplinary studies, and support of promising postdoctoral candidates will be given priority. The Foundation will fund three to five grants of \$20,000 to \$35,000 each for one year with a potential for renewal of support for an additional year. The Foundation will not fund indirect costs. Payments will be made directly to the principal investigator's institution.

### Important Dates

**December 1:** Deadline for submission of letters of intent

**December 21:** Selected applicants invited to submit full proposals (5-page maximum)

**February 1:** Deadline for submission of full proposal

**May 15:** Funding announced

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## Restless Legs Syndrome Foundation

The Restless Legs Syndrome Foundation is a nonprofit 501(c)3 organization that provides information about RLS; develops support groups; funds research to find better treatments and, eventually, a definitive cure; and publishes a quarterly newsletter known as *NightWalkers*. Annual updates to this medical bulletin are available free of charge from the RLS Foundation. In addition, the RLS Foundation provides complimentary copies of our patient-education brochure, *Living with Restless Legs*.

Your support of the RLS Foundation helps to underwrite the cost of these publications, entitles you to receive quarterly copies of our newsletter, and funds the RLS Foundation's research and education programs.

If you would like to receive brochures for your office, to receive publications, or for more information, please contact the RLS Foundation.

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Restless legs syndrome can be a serious disorder. Persons suspecting that they may have RLS should contact a qualified healthcare provider. Literature concerning RLS that is distributed by the Restless Legs Syndrome Foundation, Inc., is offered for information purposes only and should not be considered a substitute for the advice of a healthcare provider. © 2004 *Restless Legs Syndrome Foundation, Inc.*



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