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**RESTLESS LEGS
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A B S T R A C T

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 or sedative-hypnotics is of value in some RLS patients. New research with familial RLS has documented linkage to three distinct genetic loci — at 12q in several French-Canadian and German families, and the Icelandic population at large, 14q in an Italian family, and 9p in several American families. As of 2005, RLS is considered to be a complex disorder probably influenced by a variety of genetic factors and some prominent environmental causes that may operate through a variety of distinct biochemical and central and peripheral nervous system pathways.

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INTRODUCTION AND HISTORY

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.¹ For the next two centuries, RLS was mentioned only infrequently in the literature.

In the 1940s, Swedish neurologist Karl Ekbom wrote a series of detailed clinical descriptions of the disorder and coined the term restless legs syndrome.² Another major advance came when Lugaresi's group in Italy recorded periodic leg movements in sleep (PLMS) using EMG-recording electrodes attached to the legs of patients with RLS. They documented the very frequent occurrence of PLMS in patients with RLS.³

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 leg movement disorder (PLMD) in 1999.⁴

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.⁵ In the late 1970s and early 1980s, treatment with benzodiazepines was reported to be helpful in controlling the symptoms of RLS.^{6,7}

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 Akpınar, who suggested that L-dopa and other dopaminergic agents might be helpful in RLS.⁸ 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 first drug (ropinirole: Requip) was approved by the FDA for treatment of primary RLS in May 2005; other agonists may be approved in the near future. The last 20 years have also produced scientific documentation of Willis' original finding that opioids might be helpful in RLS, along with the discovery that the anticonvulsant gabapentin has beneficial impact on RLS symptoms.

Recent genetic linkage studies, including those of Rouleau's Montreal group — including Jacques Montplaisir,⁹ the Milan investigators including Zucconi and Ferini-Strambi,¹⁰ and an American group including William Ondo¹¹ — suggest there may be an important genetic contribution to the disorder. The discovery that RLS may be linked to chromosomes 12, 14 or 9, respectively, 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 functional imaging or electrophysiology studies such as those by the Munich Max Planck group (Claudia Trenkwalder)¹² or in Mark Hallett's laboratory at the NIH¹³ have sought to locate the area of the brain or spinal cord responsible for the production of PLMS and RLS symptoms. Earley and Allen at Johns Hopkins^{14,15} have documented central iron deficiency in patients with RLS through MRI and cerebrospinal fluid (CSF) studies. With Beard and Connor from Penn State, they have shown autopsy deficiencies of brain iron¹⁶ and iron regulatory proteins¹⁷ in RLS patients. They suggest that low brain iron may cause dysfunction of the dopamine system.¹⁸

PREVALENCE OF RLS

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 International Restless Legs Syndrome Study Group (IRLSSG), first promulgated in 1995.^{19,20} In a 1994 Canadian survey, 15% of respondents reported "leg restlessness at bedtime"; and 10% reported "unpleasant leg muscle sensations associated with awakening during sleep and with the irresistible need to move or walk."²¹

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.²² 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.²³⁻²⁷

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%.²⁸ In this population-based survey, Phillips and colleagues asked 1803 men and women via telephone whether they experienced symptoms of restless legs five 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% aged 80 years and older, with no difference between men and women.

Subsequent studies from Sweden,^{29,30} Chile,³¹ and Europe³² have reported similar results, while one study in Switzerland among younger individuals found a 4%

prevalence.²⁹ Two recent multinational U.S. and European countries have found that 11% of those visiting primary care practices and 7% of the general population have RLS symptoms.^{33,34} Some studies conducted on clinical populations have found higher frequencies of symptom prevalence. 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 finding has been an increase in prevalence throughout adult life, lasting through late middle age.

Studies are inconsistent as to whether prevalence in the elderly (over 65 years old) continues to increase, 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.²⁸ 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.³⁵ In Japan 5% were reported to endorse questions probing RLS,³⁶ 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,³⁷ 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. Prevalence studies based upon face-to-face interviews are more reliable but not as plentiful. Early studies by Ekbom² in Sweden and Strang³⁸ in Australia found prevalences of 5% and 3.2%, respectively, in outpatients. A more recent study using face-to-face expert interviews occurred under the auspices of 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%).³⁹

DIAGNOSTIC PROCESS & CRITERIA

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 3), and should rule out potential mimics of RLS (e.g., diabetic polyneuropathy with nighttime paresthesias, leg cramps, positional discomfort, arthritic pains) (Table 1). 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 2002, a collaboration of participants in the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health and members of the IRLSSG reviewed and revised the diagnostic criteria for RLS, along with supportive clinical features and associated features.¹⁹ These criteria are outlined below and are also outlined in Table 3.

A. ESSENTIAL CRITERIA

These primary features must be present for a diagnosis of RLS:

1. Urge to move the legs usually with dysethesias: *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.)*

Table 1 | Differential Diagnosis

Potential mimics of RLS:

1. Leg cramps
2. Peripheral neuropathy
3. Varicose veins
4. Painful legs and moving toes
5. Intermittent claudication
6. Positional discomfort
7. Neuroleptic-induced akathisia
8. Leg pains from arthritis or other disorder
9. Fidgets or nervous leg shaking

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. This being said, most patients who seek medical treatment describe both components. Patients often have difficulty describing their RLS sensations and use such broad terms as “uncomfortable” and “inside the leg”, or compare the sensations to some other feeling (Table 2). In general, two themes emerge: the sensations are perceived to originate deep inside the leg, and they 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.^{40,41} Bassetti and colleagues in Italy reported that more than 50% of their 55 RLS patients described pain as a primary component of their RLS.⁴⁰

RLS may also involve the arms or other body parts, although the sensations are almost always first noticed in the lower extremities before spreading to involve other areas.⁴² Estimates of RLS patients with symptoms in the arms range from 34%⁴² to almost 50%.⁴³ 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.^{40,44} 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,⁴⁵ 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,⁵ but in rare clinical cases a patient

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
- Creepy crawly
- Throbbing
- Like a toothache in the legs
- The “heeby-jeebies”
- Crazy legs
- “Jimmy” legs
- Painful
- Pulling
- Tearing
- Itching bones
- Growing pains

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 or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying 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).⁴³ The test evaluates periodic leg movements while awake (PLMW) and self-reported sensory symptoms in subjects instructed to remain still for one 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.⁴⁶ 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 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.⁵

Table 3 | Features of RLS

A. Essential Criteria

1. Urge to move
2. Onset or exacerbation with rest
3. Relief with movement
4. Circadian pattern

B. Supportive Clinical Features

1. Family history
2. Response to dopaminergic therapy
3. Periodic leg movements

C. Associated Clinical Features

1. Natural clinical course following certain identifiable patterns
2. Sleep disturbance
3. Normal medical evaluation/physical examination

DIAGNOSTIC PROCESS & CRITERIA (continued)

Winkelmann and colleagues found that changes of temperature represented an effective coping strategy in 82% of 300 patients.⁴² 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 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 the symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)*

In two studies, researchers were able to separate circadian effects from the impact of both recumbence and rest on symptoms of RLS.^{46,47} Over a 72-hour period, Hening and colleagues evaluated patients with fairly severe RLS for motor restlessness,⁴⁷ and Trenkwalder and coworkers evaluated a similar group of patients for PLM.⁴⁶ Both studies included polysomnographic recordings taken after both normal sleep and one and a half days 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 a.m. to 11 a.m.). 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.

B. SUPPORTIVE CLINICAL FEATURES

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.^{42,45,48,49}

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.⁵⁰⁻⁵⁸ This initial response, however, is not universally maintained.

3. Periodic leg movements (during wakefulness or sleep)

Periodic leg movements in sleep (PLMS) occur in about 80% of people with RLS;⁵⁹ however, PLMS is also common in conjunction with other disorders and among the elderly.⁶⁰⁻⁷²

C. ASSOCIATED CLINICAL FEATURES

These features may provide additional information about the patient's diagnosis:

1. Natural clinical course following certain identifiable patterns

Multiyear, prospective case control studies have not been completed. Retrospective analysis indicates that 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.^{40,45,73} 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.⁴⁸ 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,^{74,75} and postpartum in women with RLS occurring in pregnancy.⁷⁶ 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,⁷⁶ which is itself substantially above the background rate of the population. As will be further addressed, 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. This being said, given the extremely long periods required for correcting iron deficiency, it is hard to envision how this hypothesis can account for the extremely rapid improvement of RLS seen after renal transplantation or postpartum.

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.^{48,77,78} 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, generally show a slower progression of symptoms.⁴⁵

2. Sleep disturbance

Disturbed sleep is the 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 state of sleep is a time of susceptibility to RLS symptoms, and the methods used to relieve the symptoms are likely to interfere with sleep. Thus, RLS interferes with both initiation and maintenance of sleep. A patient with moderate to severe RLS may average less than five 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.⁷⁹ Reduced sleep efficiency correlates with the reported clinical severity of RLS.³⁷ 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. Normal 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,

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association and may require different approaches to treatment.⁴⁵

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. It is incumbent upon initial and follow-up visits for the physician to assess for these conditions either by history or formal laboratory testing. 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 to the occurrence of RLS.^{80,81} Measurement of serum ferritin level and percent iron saturation is now considered part of the standard medical evaluation for RLS.

The recent expansion of knowledge about the pathophysiology of RLS can be roughly divided into three areas:

1. Anatomic Localization of Dysfunction Associated with RLS
2. Neurotransmitter Systems Involved in RLS
3. Iron Metabolism in RLS

1. 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 reducing⁸² and antagonists exacerbating⁸³ 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.⁵⁵ 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,^{65,84,85} 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 transaction by only about 30%⁸⁴ compared with the 80% to 100% reduction seen for the PLM with RLS.^{12,86}

Spinal pacers appear to contribute to the observed periodicity of limb movements seen in RLS; independent pacemakers could also account for the different periodicities sometimes noted in different limbs of the same patient,^{87,88} but these alone do not suffice to explain the phenology 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.^{89,90} 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.⁹¹ 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.¹³

These results 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 the brainstem's 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.⁹² Transcranial magnetic stimulation studies have found that, compared with controls, RLS patients show reduced intracortical inhibition for both foot and hand⁹³ and an increased cortical silent period without other changes.⁹⁴ These findings suggest abnormal brainstem (i.e., 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.¹²

Finally, one study reports results from lesions of the subcortical A11 dopamine system in rats.⁹⁵ This A11 dopamine system includes the cell bodies for the spinal dopamine neurons that may be modulating nociceptive responses.⁹⁶ 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.

2. Neurotransmitter Systems Involved in RLS Brain Dopaminergic Function in RLS

Both Akpinar⁸ and Montplaisir and colleagues⁹⁷ somewhat serendipitously discovered that low doses of levodopa provide almost complete relief — at least temporarily — 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 comparatively low doses of these medications supports the concept that RLS may involve abnormalities in dopaminergic function. There have also been six PET or single photon emission computed tomography (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.⁹⁸ 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,⁹⁹ but showed reduced binding in the other two studies.^{100,101} This is a confounding variable because of the known decrease in D2R with age.¹⁰² In the other studies, however, the subjects and controls were age-matched.⁹⁸ Two of the SPECT studies^{100,101} also reported no difference between RLS patients and controls for dopamine transporter (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 dopamine (DA) pathway that exists during the asymptomatic period. Moreover, none of these studies measured D2 Bmax, the D2 release, or 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 putamen⁹⁸ and only one showed a change (10% less uptake in RLS patients) in the caudate.¹⁰¹ 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.¹⁰³ 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.

PATHOPHYSIOLOGY OF RLS (continued)

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.^{104,105} 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.⁷⁵ 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.

3. Iron Metabolism in RLS

The three major, reversible secondary forms of RLS — pregnancy, end-stage renal disease (ESRD), and iron deficiency anemia — are associated with iron insufficiency. All conditions that seemingly produce problems with inadequate iron also produce RLS, suggesting that the iron insufficiency may be a significant feature of the disorder. Serum levels of ferritin, the primary storage unit for iron, have been found to correlate inversely with RLS severity.^{80,81} In one study, CSF levels of ferritin were low and transferrin levels high for RLS patients compared with age-matched normal subjects;¹⁵ 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.^{14,103} Treatment with iron, either orally⁸¹ or intravenously,¹⁰⁶ has been found to improve or even 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.¹⁰⁷ Orally administered iron supplements can sometimes correct iron deficiency and reduce RLS symptoms.⁸¹ 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 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,¹⁰⁸ decreased dopamine transporter,¹⁰⁹ and increased extracellular dopamine.^{110,111} 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, an autopsy study evaluated the brains from seven RLS subjects and five age-matched controls.¹⁶ Standard pathologic assessment showed no gross abnormalities in numbers of cells, general cell distribution, or morphology. However, a histological 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. Another autopsy study using quantitative techniques in neuronal cells from the substantia nigra also showed that despite the low iron state, transferrin receptor concentration was not increased as would normally be expected. The study also found that a special protein called Iron Regulatory Protein 1 (IRP 1), which controls synthesis of transferrin receptor, had diminished levels and activity.¹⁷ The findings indicate that in at least some proportion of patients with RLS decreases in brain iron may contribute to the syndrome and that these changes in brain iron may occur because of problems with the iron regulatory proteins.

GENETICS OF RLS

A strong familial component in RLS has been suspected since Ekblom published his seminal description of the disorder in 1945.² Surveys are consistent in revealing that 40% to 60% of first-degree relatives of RLS patients are similarly affected.^{42,45,48} Common features shared by individuals with familial RLS include symptom onset before age 30, worsening during pregnancy, and aggravation by alcohol.⁴² The mode of inheritance seems to be autosomal dominant.¹¹² 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 twins¹¹³ despite reports that expression of the full RLS spectrum (e.g., onset of symptoms) can vary between twins and within families.¹¹³⁻¹¹⁵ Many other cases of RLS — best characterized as "sporadic" — typically appear in later life and cannot be so readily identified as familial. In this sporadic group, 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. Preliminary findings are nonetheless promising, and the hunt for causative genes has been taken up by several groups within several genetically distinct populations across the world (in Canada, Italy, Germany, U.S., and Iceland). The first major susceptibility locus for RLS was reported on a region on the long arm of chromosome 12 (designated RLS1) in a study of a single French-Canadian family in Quebec¹¹⁶ and has recently been confirmed in additional 5 of 18 families,¹¹⁷ and extended to a study of 100 families in Iceland.¹¹⁸ A second susceptibility locus for RLS designated RLS2 on the long arm of chromosome 14 (14q) was identified initially in two large families from South Tyrol¹¹⁹ and subsequently in a single French-Canadian family.¹²⁰ This locus was the first reported with an autosomal dominant mode of inheritance.¹⁰ Finally, a third locus for RLS, designated RLS3 and also demonstrating a dominant mode of inheritance, has been identified in two large families from the United States on the short arm of chromosome 9p.¹¹ Of particular relevance in the most recent French-Canadian, Italian, and Icelandic studies was recognition of periodic leg movements of sleep (PLMS) as a critical 'endophenotype' for RLS; viz., that the phenotypic spectrum in many families includes periodic leg movements lacking subjective appreciation of restless legs. Thus, RLS appears increasingly to be a

complex disorder influenced by many genetic factors (rather than a single hereditary component). Given the intensity of research in diverse populations, the future promises to yield exciting new information about about specific genes that modify expression of RLS. Ultimately, this will lead to increased recognition of and improved treatments for RLS.

TREATMENT RECOMMENDATIONS

"An Algorithm for the Management of Restless Legs Syndrome" was published in the July 2004 edition of *Mayo Clinic Proceedings* and is reprinted in part here. This algorithm was developed by the Medical Advisory Board of the Restless Legs Syndrome Foundation and was the first algorithm produced by the consensus of a group of experts. The algorithm was designed to specifically aid primary care physicians in treating patients diagnosed with RLS.¹²¹ Letters following recommendations indicate subsequent comments.

Table 4

INTERMITTENT RLS

Intermittent restless legs syndrome is defined as RLS that is troublesome enough when present to require treatment but does not occur frequently enough to necessitate daily therapy.

Nonpharmacological	Pharmacological
Consider determining the serum ferritin level. If the serum ferritin level is low, administer iron replacement. (A)	Carbidopa/levodopa, 25 mg/100 mg, or controlled-release (CR), 25 mg/100 mg (C)
Recommend mental alerting activities, such as video games or crossword puzzles, to reduce symptoms at times of boredom.	Dopamine agonists, such as pramipexole or ropinirole (D)
Consider a trial of abstinence from caffeine, nicotine, and alcohol.	Low-potency opioids, such as propoxyphene or codeine, or opioid agonists, such as tramadol (E)
Consider whether antidepressants, neuroleptic agents, dopamine blocking antiemetics such as metoclopramide or sedating antihistamines (including those found in nonprescription medications) may be contributing and whether discontinuation is possible without causing patient harm. (B)	Benzodiazepines or benzodiazepine receptor agonists, such as temazepam, triazolam, zolpidem, zaleplon, or eszopiclone (F)

DAILY RLS

Daily restless legs syndrome is defined as RLS that is frequent and troublesome enough to require daily therapy.

Nonpharmacological	Pharmacological
The nonpharmacological approach for daily RLS is the same as for intermittent RLS.	Dopamine agonists, such as pramipexole or ropinirole (G)
	Gabapentin (H)
	Low-potency opioids, such as tramadol (I)

REFRACTORY RLS

Refractory restless legs syndrome is defined as daily RLS treated with a dopamine agonist with one or more of the following outcomes: (1) inadequate initial response despite adequate doses (2) response that has become inadequate with time, despite increasing doses (3) intolerable adverse effects (4) augmentation that is not controllable with earlier doses of the drug.

Nonpharmacological	Pharmacological
Helpful nonpharmacological approaches should be continued in addition to pharmaceutical treatment.	Change to gabapentin. (H)
	Change to a different dopamine agonist. (J)
	Add a second agent such as gabapentin, a benzodiazepine, or an opioid. (K)
	Change to a high-potency opioid or tramadol. (L)

A. Because RLS may be the only clinical indication of iron deficiency, clinicians should determine the serum ferritin level in all patients with RLS, especially those with a history of gastrointestinal blood loss, disorders or medications predisposing to gastrointestinal blood loss, menorrhagia, frequent blood donation, or recent onset or worsening of symptoms. If the serum ferritin level concentration is in the abnormal range for the specific laboratory (usually <20mcg/L) or percent iron saturation is low (generally <20%), a cause of iron deficiency should be pursued and replacement treatment instituted. A serum ferritin concentration lower than 45 to 50mcg/L has been associated with an increased severity of RLS,^{80,81} and therapy can be attempted in patients with levels in this range on a case-by-case basis. A common regimen is 325 mg of ferrous sulphate three times a day in combination with 100 to 200 mg of vitamin C with each dose to enhance absorption. Oral iron therapy can cause constipation and abdominal discomfort, and the dose may need to be reduced in some patients. Iron tablets should ideally be taken on an empty stomach to enhance absorption, but if gastrointestinal symptoms develop, they should be taken with food. Iron should not be prescribed empirically because it may result in iron overload, especially in patients with previously unsuspected hemochromatosis. Follow-up ferritin determinations are needed, initially after 3 to 4 months and then every 3 to 6 months until the serum ferritin level is greater than 50mcg/L and percent iron saturation is greater than 20%. Iron therapy can then be discontinued, but follow-up serum ferritin determinations are recommended to ensure that levels do not decrease, especially if RLS symptoms worsen. Of note, RLS does not always respond to an increasing serum ferritin concentration, even if it was low initially.

B. Clinical experience suggests that most antidepressants may sometimes be associated with initiation or worsening of RLS. However, if antidepressants are deemed necessary, the symptoms can usually be treated in the same way as primary RLS. Alternatively, use of bupropion can be considered because this antidepressant has been shown to reduce periodic leg movements in depressed patients and thus may be less likely to induce or worsen RLS.¹²²

C. Carbidopa/levodopa, 25 mg/100 mg (½-1 tablet), can be used for RLS that occurs intermittently in the evening, at bedtime, or on waking during the night or for RLS associated with specific activities, such as airplane or lengthy car rides or theater attendance. Controlled-release

carbidopa/levodopa, 25 mg/100 mg (1 tablet), can be used alternatively before bed for RLS that awakens the patient during the night. Even the CR form has a relatively short duration of action and may not produce sustained efficacy if RLS persists throughout much of the night. Controlled trials have shown efficacy of both preparations.^{82,123} For maximal absorption, levodopa should not be taken with high-protein foods.

Problems with levodopa treatment include augmentation and rebound. Augmentation is defined as a worsening of RLS symptoms earlier in the day after an evening dose of medication, including earlier onset of symptoms, increased intensity of symptoms, or spread of symptoms to the arms.¹²⁴ Up to 70% of patients taking levodopa daily will develop augmentation, and the risk increases with daily doses of 200 mg or more.¹²⁵ The risk of augmentation may be lower with intermittent use, such as fewer than three times a week, but this has not been established firmly. Patients should be warned about the phenomenon because taking additional doses of levodopa worsens augmentation. Augmentation has also been reported with newer dopamine agonists but at a much lower frequency than with levodopa (generally 10 to 25% at 1 to 2 year follow-up) (see F). This remains an inadequately studied area which has attracted increased interest with respect to enhancing its recognition and treatment. Treatment/correction of augmentation requires highly individualized treatments — often at tertiary referral centers familiar with RLS — that remain largely empiric in nature. If augmentation occurs, the offending drug should be discontinued rather rapidly (over 3 to 4 days) and another agent of the same or different pharmacologic class substituted. Combination therapy with a variety of drugs from different classes may eventually be necessary, possibly necessitating retention of the very smallest incremental dose of the original, offending dopamine agent. Rebound, the recurrence of RLS in the early morning, occurs in 20% to 35% of patients taking levodopa.^{125,126}

D. The action of dopamine agonists generally commences 90 to 120 minutes after ingestion; thus, these agents cannot be used effectively once symptoms have started.

E. Intermittent use of low-potency opioids or opioid receptor agonists, usually before bed, can be effective. Doses of 100 to 200 mg of propoxyphene napsylate, 65 to 130 mg of propoxyphene hydrochloride, 30 to 60 mg of codeine, usually available in combined preparations

TREATMENT RECOMMENDATIONS (continued)

with acetaminophen, or 50 to 100 mg of tramadol can be taken before bed or during the night. Constipation or nausea may occur.

F. Intermittent use of benzodiazepines or benzodiazepine receptor agonists before sleep may be useful, especially if the patient has another cause of poor sleep in addition to RLS, such as psychophysiologic insomnia. Short-acting agents, such as triazolam (0.125-0.5 mg), zolpidem (5-10 mg), or zaleplon (5-10 mg), may be helpful for sleep-onset insomnia caused by RLS; intermediate-acting agents, such as temazepam (15-30 mg), or eszopiclone (1-3 mg) may be helpful for RLS that awakens the patient later in the night. Most controlled trials have been performed with clonazepam (0.5-2 mg).⁸² Although some investigators have shown this drug to be well-tolerated in older patients,¹²⁷ its long duration of action may result in more adverse effects, such as unsteadiness during the night and drowsiness or cognitive impairment in the day.

G. Dopamine agonists are the drugs of choice in most patients with daily RLS.^{82,123,128,129} The nonergot agonists such as pramipexole and ropinirole are generally preferred to the ergot agonists such as pergolide because of their more favorable adverse-effect profile. Pramipexole is usually commenced as 0.125 mg once daily, taken two hours before major RLS symptoms start. The dose is increased by 0.125 mg every 2 to 3 days until relief is obtained. Most patients require 0.5 mg or less, but doses up to 2 mg may be needed. Ropinirole is usually commenced as 0.25 mg 1 to 3 hours before symptoms presentation and is increased by 0.25 mg every 2 to 3 days. Most patients require 2 mg or less (note that higher equivalent doses are needed compared with pramipexole), but doses up to 4 mg or higher may be needed. Some patients require twice-daily doses of agonists when early evening symptoms are present, typically given as an earlier dose in the late afternoon or early evening and a second dose before bed. The action of dopamine agonists generally commences 90 to 120 minutes after ingestion; thus, these agents cannot be used effectively once symptoms have started.

Augmentation is less common with these drugs than with levodopa but may occur in about one-third of patients taking pramipexole for two years.^{130,131} Equivalent data for ropinirole are not available. In contrast to levodopa, augmentation can usually be managed in many patients, at least initially, by additional doses of the drug earlier in the day. An alternative approach is to switch to another

medication. Adverse effects of the agonists include nausea and light-headedness that usually resolve within 10 to 14 days. Nasal stuffiness, constipation, insomnia, and leg edema occur less frequently and are reversible with cessation of treatment. Hypersomnia appears less common than when the drugs are used to treat Parkinson's disease,¹³² perhaps because of the lower doses used.

H. Gabapentin may be an alternative choice, particularly in less intense RLS, RLS perceived as painful, RLS in combination with a painful peripheral neuropathy or unrelated chronic pain syndrome, or RLS in association with neurodegenerative disorders such as Parkinson's disease or dementia. Unless RLS occurs throughout most of the day, gabapentin should be used as once- or twice-daily doses in the late afternoon or evening or before sleep. Treatment should commence at 100 to 300 mg per dose because of the tendency of the drug to cause somnolence and gait unsteadiness, especially in elderly patients. A controlled trial has suggested that mean doses of 1300 to 1800 mg/d are needed for efficacy,¹³³ but many patients appear to benefit from lower doses. If gabapentin is unsuccessful or poorly tolerated, a dopamine agonist should be considered next, if not already tried.

I. Low-potency opioids may be an alternative choice. (See comment E for dosage schedules.) If low-potency opioids are unsuccessful, use of a dopamine agonist should be considered, if not already tried.

J. Patients often show different responses to other dopamine agonists when a suboptimal response has been obtained with one agent. Adverse effects and efficacy may vary, and the development of augmentation with one agent does not necessarily predict augmentation with a different drug, at least initially.¹³⁰ Ropinirole or pramipexole can be substituted for each other, and occasionally pergolide can be used, although adverse effects are generally more frequent, including rare reports of ergot-related pleural or cardiac valvular fibrosis, or fibrosis of other organ systems. A dose of 0.05 mg of pergolide is equivalent to 0.125 mg of pramipexole, and most patients respond to a daily dose of about 0.2 mg. If augmentation develops with a second dopamine agonist, a change to a different class agent is mandatory.

K. (See previous comment F, H, I). Long-term use of benzodiazepines may lead to dependency, but these drugs

TREATMENT REVIEW (continued)

that require walking, such as housework or exercise, may help relieve RLS symptoms if delayed until later in the day. Women who find that their RLS symptoms are worsened during the week prior to menstruation may want to avoid sedentary activities at that time. If they are on hormonal therapy (estrogen/progesterone) they may benefit from a change in therapy. There are many anecdotal reports of sexual stimulation and especially orgasm relieving RLS symptoms which works well for many who cannot fall asleep due to RLS.

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,¹³⁵ conditioning therapy,¹³⁶ and various procedures to reduce incompetent veins,¹³⁷ 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.¹³⁸ The newest potential treatment for RLS, currently used for refractory angina, congestive heart failure, and vascular impotence, is called Enhanced External Counter Pulsation (EECP).¹³⁹ EECP involves inflation and deflation of three sets of compressive cuffs wrapped around the patient's calves, lower thighs, and upper thighs. This preliminary study demonstrated promising results but follow-up studies are necessary to prove its effectiveness.

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 anti-nausea agents, 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 after 3:00 p.m. Alcohol may initially afford temporary relief from restlessness and promote sedation, but after 30 to 90 minutes, this effect dissipates and may be superceded by rebound sympathetic drive and worsening of leg restlessness and sleep disturbance symptoms.

Tricyclic and serotonin reuptake blocking antidepressants

often intensify symptoms of RLS.⁶⁸ Paradoxically, some patients respond favorably to these same antidepressants. (Theoretically, these positive responses might reflect amelioration of an anxiety, stress, or sleep deprivation-induced worsening of RLS, conditions for which antidepressants may be useful. This being said, such etiologic connections to RLS have not yet been convincingly demonstrated.) Bupropion, a dopamine-active antidepressant, may prove to be the most preferred antidepressant, as a study in five patients with PLMS showed a reduction in leg movements on sustained-release bupropion.¹²²

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.

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 investigation noted that metoclopramide, when used in the afternoon, worsened restlessness for most of the drug-naïve research subjects with RLS.⁸³ In general, antiemetic medications that inhibit the dopamine system, such as prochlorperazine or chlorpromazine, may markedly exacerbate restlessness.^{140,141} This interaction can create a problem when a patient with RLS undergoes 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 antiemetic medications, granisetron hydrochloride and ondansetron hydrochloride, are selective 5-HT₃ receptor antagonists with little or no affinity for other receptors, including dopamine receptors.¹⁴² 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.^{67,143} In addition, there have been reports of severe exacerbations of RLS after intravenous

droperidol anesthesia,¹⁴⁴ 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 Therapies

The first drug to receive FDA approval in the U.S. for the treatment of RLS is ropinirole (Requip), which was approved on May 5, 2005. In addition to the use of ropinirole, 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 professional meeting and abstracted in a major journal. Restex (carbidopa/benserazide) has been approved in Germany and Switzerland for the treatment of RLS.

Table 5 | Pharmacologic agents for treatment of RLS

- A. Dopaminergic agents
 - 1. Dopamine precursors
 - 2. Dopamine receptor agonists
 - a. Ergotamine dopamine agonists
 - b. Nonergotamine dopamine agonists
- B. Opioids
- C. Benzodiazepines and other sleeping aids
- D. Anticonvulsants

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, high doses 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, particularly in refractory cases. 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 trying 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.

A. Dopaminergic Agents

Dopaminergic agents that increase the level of available synaptic dopamine are classified as dopamine precursors (e.g. levodopa), while those acting directly upon dopamine receptors are classified as dopamine receptor agonists. The latter group is increasingly recognized as the mainstay of pharmacologic therapy.

1. 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 divided doses before bedtime and during the sleep period.¹⁴⁵⁻¹⁴⁷ The effectiveness of the drug to relieve RLS and reduce PLMS was clearly demonstrated, leading to consider levodopa as a guideline treatment for RLS. Side effects include gastrointestinal discomfort, nausea and vomiting, and headache. The more common problems with the levodopa treatment in RLS are daytime augmentation, early morning rebound, and, to a lesser extent, daytime sleepiness. The short half-life of the drug provokes a relief of RLS and PLMS confined to the first 4 to 6 hours, compounded by the tendency of symptoms to recur later, often leading to poor sleep quality.⁵⁰ Recent studies confirm the effect of levodopa and reported that the combination of regular (100-200 mg) and slow release (100-200 mg) doses before bedtime provides a longer duration response compared to regular release levodopa¹⁴⁸ alone. Effectiveness on the first night of usage supports the feasible intermittent or as needed use of levodopa. Moreover, the near-immediate onset of action realized with levodopa 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.^{149,150}

TREATMENT REVIEW (continued)

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.¹²⁴ It is most common (20-35%) with the use of short-acting preparations and at higher dose levels.

Augmentation is the tendency for symptoms to develop earlier in the day (e.g., morning or late afternoon instead of mid-evening) and to be more severe than the symptoms that occurred before treatment with carbidopa/levodopa began.¹²⁵ Most recent experience suggests that augmentation can be a complicating feature in 65% to 80% of cases, as early as four weeks into treatment. 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.

2. Dopamine Receptor Agonists

Dopamine agonists act via activation of central dopamine 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 augmentation and rebound as compared with levodopa treatment.

a. Ergotamine Dopamine Agonists

Pergolide

Several open-label^{125,151,152} and randomized, double-blind, placebo-controlled trials^{53-55,153} have shown efficacy with pergolide in the treatment of RLS. 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 remaining two patients had a "nearly complete relief" on pergolide,

with only one patient in the levodopa group achieving "complete relief of nighttime restlessness."⁵⁴ 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.⁵³ 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 one hour before bedtime. Wetter et al. used a protocol similar to that of Winkelmann et al. (domperidone three times a day in conjunction with a 2-hours-before-bedtime, single dose of pergolide) in 30 patients with idiopathic RLS who had remained psychotropic-drug free for two weeks before and during enrollment in the study.⁵⁵ 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 one-year open-label follow-up from this study showing that 22 of the 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 followup.¹⁵⁴ The most recent study of 100 patients by Trenkwalder and colleagues showed that after six weeks of treatment with 0.25 to 0.75 mg/d compared to placebo there was improved RLS severity and a reduction in PLMS. In the second phase of the study patients were treated for one year and improvements were maintained.

In summary, pergolide — given either as a single dose before bedtime or in divided doses in the late afternoon or evening and one 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.). However, there have been recent reports of pergolide potentially causing valvular heart disease¹⁵⁵⁻¹⁵⁸ and thus the current recommendations are not to use pergolide unless other treatments have been exhausted. Fibrosis of cardiac valves, and pleural and retroperitoneal tissues are increasingly

recognized, albeit rare, irreversible side effects of treatment with all ergot-derived medications. Thus, if they are employed, six-month evaluations with echocardiography and chest X-rays have been advocated, for example, in Parkinson's disease where these agents are used at much higher dosages.

Cabergoline

A second ergot dopamine agonist studied in RLS is cabergoline. While available in the United States to treat hyperprolactinemia, it is prohibitively expensive and not prescribed for RLS. Stiasny-Kolster and colleagues in Europe have shown in a double-blind, placebo-controlled study of 85 patients that doses of 0.5 to 2.0 mg/day were effective at reducing RLS symptoms during the day and night.¹⁵⁹ Rates of adverse events, including augmentation, were reported as low, and being an ergot-derived medication, it is deserving of the same warnings attending use of pergolide (see above).

b. Nonergotamine 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.

Ropinirole

Ropinirole is a nonergotamine dopamine agonist whose efficacy in treating RLS has been well-established. Multiple open-label and double-blind, placebo-controlled studies have now been published.¹⁶⁰⁻¹⁶⁴ 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).^{161,162} In a small crossover trial by Adler and colleagues¹²⁹ of 22 patients treated with ropinirole and placebo, there was a significant improvement in the RLS rating scale score when the patients took ropinirole. Eight of the patients had complete resolution of symptoms on ropinirole. The dose was started at 0.25 mg at dinner and bedtime with a maximum of 3 mg at each time point.

Allen and colleagues¹⁶⁵ studied 65 patients with RLS and PLMS. They treated patients with placebo or 0.25 to 4.0 mg of ropinirole per day for 12 weeks. There was a significant marked reduction in PLMS per hour that overwhelmed a near statistically significant improvement from subjective

perception of restlessness as revealed by the IRLSSG scale. The latter was principally due to a seemingly high favorable response to this subjective metric in the placebo arm of the study. Headache, nausea, and dizziness were more common on ropinirole.

Trenkwalder and colleagues¹²⁸ recently published their trial of 284 subjects randomized to placebo or ropinirole. At the end of 12 weeks, the average ropinirole dose was 1.9 mg/d (single dose at 1 to 3 hours before bedtime), and there was greater improvement of the RLS rating scale score in those on ropinirole than those on placebo. While a large placebo response was found, ropinirole effect was even greater. The major side effects were nausea and headache.

In an open-label crossover comparison of ropinirole vs controlled-release carbidopa/levodopa (each used for six weeks) in 11 patients, Pellecchia and colleagues¹⁶⁶ found ropinirole to be superior in subjective response and increasing sleep time. One patient had severe vomiting on levodopa.

In summary, recent well-controlled studies have shown ropinirole, given as a single bedtime dose or at dinner and bedtime, is effective treatment for the RLS and PLMS. The initial dose is typically 0.25 mg before bedtime or at dinner and bedtime and is titrated upward every 2 to 3 days in order to avoid common side effects such as nausea and orthostatic hypotension. The average patient responds to a total dose in the 1.0 mg/d to 2.5 mg/d range (mean effective dose from numerous studies ~ 2.0 mg). RLS patients typically habituate to side effects in a matter of 7 to 10 days. Other occasional side effects include fatigue or sleepiness. Long-term efficacy and the degree of augmentation of ropinirole have not been established.

Pramipexole

Two open-label trials and one double-blind, randomized, crossover trial of pramipexole in the treatment of RLS have recently been published.¹⁶⁷⁻¹⁶⁹ Lin et al. treated 16 patients without adverse events.¹⁶⁷ 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, three-month study that included 23 patients who had received a variety of previous treatments for RLS.¹⁶⁸ Nineteen patients reported significant improvement and remained on

TREATMENT REVIEW (continued)

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 ten RLS patients in a one-month double-blind, placebo-controlled crossover fashion.⁵⁶ Leg discomfort was alleviated at bedtime and during the night, both objectively and subjectively. In some cases there was complete resolution of symptoms 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 seven patients demonstrated the safety and long-term efficacy of pramipexole.¹⁷⁰ In a retrospective review of 60 patients treated with pramipexole, Silber and colleagues¹³⁰ found that 94% of patients had complete or partial benefit from pramipexole at a median dose of 0.63 mg/d after a mean follow-up of 27.2 months. Eleven patients discontinued drug and the most common side effects were insomnia, nausea or dyspepsia, and dizziness. Augmentation developed in 33% of the cases.

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. The mean effective dose from multiple studies is approximately 0.375 mg. 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 possibly 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.

Rotigotine

While not yet FDA approved for Parkinson's disease, a new dopamine agonist patch was tested in 63 patients with RLS. The double-blind, placebo-controlled study evaluated effects after only one week of treatment. Stiasny-Kolster and colleagues found that at all doses tested (1.125 mg, 2.25 mg, and 4.5 mg patches), the RLS severity

improved.¹⁷¹ A large clinical trial is currently underway to investigate long-term efficacy of rotigotine in RLS. Once this patch is approved for Parkinson's disease then it may be possible to use for RLS as is being done with oral formulations of the dopamine agonist agents discussed earlier.

B. Opioids

Opioid medications, also known as narcotics, have long been known to bring relief from restless legs syndrome. In fact, the use of opioids for RLS symptoms was first described by Willis in the 17th century.¹⁷² 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 two-week treatment arms.¹⁰⁴ 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 ten-day treatment arms.⁸⁶ 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.¹⁷³⁻¹⁷⁵ Meperidine and propoxyphene may compare negatively with other opiates¹⁷⁵; 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), hydromorphone (P), methadone (P), oxycodone (P); and morphine. Opioids given intrathecally via infusion pump have also been reported to improve RLS.¹⁷⁵ 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. Epidural morphine was successful in a single case.¹⁷⁶ For very severe patients, oral methadone has been found to be useful because of its long half-life.¹⁷⁷ For milder cases, the opioid-like substance tramadol has been successful in open-label studies.¹⁷⁸ The addiction potential of tramadol is low enough that it is prescribed as a non-controlled substance in the United States.

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. 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.^{145,179}

Narcotic medications are usually well-tolerated, and demonstrate good long-term efficacy, relatively low addiction potential, and little tolerance in the RLS population.¹⁰⁵ 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.

C. Benzodiazepines and other sleeping aids

Benzodiazepine medications are well suited for treatment of mild to moderate RLS with symptoms restricted to evening and nighttime hours. Nevertheless, the therapeutic effects of benzodiazepines in RLS are less studied, while most investigations have focused on PLMS. Like all RLS medications, the precise mechanism of action is unknown. However, in addition to relieving symptoms, they help sleep initiation and sleep consolidation, sleep architecture, and PLMS. Clonazepam is the longest used, although it has undergone relatively limited study. In a Japanese, open-label, sleep laboratory study of 15 RLS patients with PLMS who were treated with 0.5-1.5 mg of clonazepam for a mean duration of 21 days, RLS symptoms improved in all of the patients and PLMS decreased significantly.¹⁸⁰ In a short-term, placebo-controlled sleep laboratory study of 10 RLS and 16 PLMD patients, 1 mg of clonazepam exhibited rapid therapeutic effect in PLMS, RLS symptoms, and insomnia.¹⁸¹ Clonazepam (0.25-2.0 mg) and temazepam (15-30 mg) are typical bedtime doses. Follow-up for side effects, particularly daytime lethargy and sedation, is necessary. Clinical experience suggests that some patients benefit from benzodiazepine therapy for RLS, but compelling data in long-term studies is lacking. The treating physician must base patient selection on careful

consideration as benzodiazepines carry potential for adverse effects of dependence, cognitive disturbance, somnolence, and ataxia.

Whenever controlled substances such as benzodiazepines and opioids are prescribed, screening for history of inappropriate use, abuse and dependency needs to be explored. Patients who have a history of misuse of controlled substances are at greater risk for abuse. And yet, comprehensive reviews of the benzodiazepine literature conclude that inappropriate use, psychological dependence, and physiologic tolerance are generally uncommon during the monitored administration of these agents. In a long-term study of 170 adults who were treated for various sleep disorders, 136 patients received 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 to elderly and younger patients alike. During this study, benzodiazepine withdrawal symptoms typically did not develop at the time of gradual dose reduction or upon drug discontinuation.¹²⁷ In low to moderate dosage of longer half-life benzodiazepines (clonazepam and temazepam) the risk of dependence and addiction is low although the long-term benefit and risk for benzodiazepines in RLS patients remains to be studied. Clonazepam has also been used for treatment of short-acting benzodiazepine dependence.¹⁸²

Somnolence and cognitive disturbance occurs in 5% to 15% of patients even at low dosages of these longer acting benzodiazepines. Alternatives include a shorter acting benzodiazepine such as triazolam (0.125-0.25 mg) or a benzodiazepine receptor agonist hypnotic such as zolpidem (5-10 mg). Zolpidem has been found to be effective in one open-label study involving a small population of middle- and late-onset RLS patients.¹⁸³

Daytime clonazepam has been used in a variety of disorders: seizures, anxiety, panic disorder, and depression. Daytime use of clonazepam is best reserved for patients who have associated anxiety disorders who cannot use antidepressants as treatment. Although agreement among experts is not present, some advocate that daytime clonazepam may have a role as adjunctive therapy in refractory RLS. As frequency and dosing of clonazepam increase, so will the risks

TREATMENT REVIEW (continued)

of falls, excess sedation, and cognitive disturbance increase.

Another factor that may be a consideration in therapy is cost. For some patients, the low cost of clonazepam, temazepam, or triazolam may prove attractive. Physicians must weigh the various risks and benefits of therapy in the life of the patient, prescribing therapy that maximizes the patient's quality of life.

D. Anticonvulsants

Among the most promising new anticonvulsants for RLS treatment is gabapentin.^{184,185} In a double-blind placebo-controlled crossover study of 24 patients with two weeks for each treatment arm and one-week washout between treatments, gabapentin significantly reduced the subjective RLS symptoms as well as the PLMS during sleep.¹³³ A particular improvement of sleep was observed during treatment with gabapentin. Divided daily doses were used, and the mean effective daily dose was 1855 mg. It should be noted that the patients in this study had more moderate than severe RLS, suggesting that higher doses may be necessary in the more severely affected. 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 moderate to severe 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 five-week period. It was effective in reducing subjective symptoms of RLS.¹⁸⁶ 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 under carbamazepine failed to match the dramatic improvement in PLMS reported for the dopaminergic medications, and the adverse effects have led to limited acceptance of carbamazepine 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.^{187,188}

Other Agents

Drugs mentioned in this section are agents whose efficacy is less well-established. 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,⁵³ but other groups have been less impressed with its efficacy.⁷⁵ Typical doses for therapy are 5 to 15 mg, and side effects are similar to those associated with the use of pergolide. Apomorphine, administered parenterally, has been shown to decrease PLMS and RLS in a small number of subjects in open label studies.¹⁸⁹⁻¹⁹¹ In one study of nine patients, the PLM index fell for four hours after a single dose of subcutaneous apomorphine administered at bedtime.¹⁹⁰ In another study, subjective RLS and periodic leg movements of wakefulness were measured in nine patients during an intravenous infusion of apomorphine in a suggested immobilization test. RLS symptoms fell by 55% and PLMW by 98%.¹⁹¹ 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.¹⁹²⁻¹⁹⁴ Baclofen was found in a double-blind study to reduce arousals related to PLMS primarily by decreasing the arousal response to movements.¹⁹⁵ 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.¹⁹⁶ Another open-label study found that amantadine (100 to 300 mg per day) benefited 11 of the 21 patients who were treated.¹⁷⁸ 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.¹⁹⁷ Paradoxically, many of these same medications may exacerbate RLS symptoms, and the use of these medications cannot be recommended with any confidence.

SECONDARY RLS

Pregnancy

RLS also frequently occurs initially or is exacerbated during pregnancy. Ekblom'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.¹⁹⁸⁻²⁰⁰ Goodman found that 97 of 500 women (19.4%) with singleton pregnancies had RLS.²⁰¹ 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, Winkelman 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.⁴² Manconi and colleagues²⁰² surveyed 642 pregnant women at the time of delivery and then at follow-up appointments and found 26% met the IRLSSG criteria for RLS. Symptoms were much greater in the third trimester of the pregnancy and were associated with lower hemoglobin levels. 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),^{76,203} and one found lower ferritin levels before conception (but not during pregnancy) in women who eventually developed RLS during pregnancy.⁷⁶ For more information, please see the separate booklet, *Pregnancy and RLS: Vital considerations in treating a pregnant patient who has restless legs syndrome (RLS)*.

Uremia (End-Stage Renal Disease)

It has been recognized for over 40 years that, in comparison to the general population, RLS is more common in individuals with ESRD both before and after the institution of dialysis.²⁰⁴ Recent prevalence studies indicate that the rates of RLS among this patient group range from 6% to 83%,²⁰⁵⁻²¹² with variability likely related to differences in the diagnostic criteria used. In addition, false negatives and positives may both be common because of individual differences in the self-appraisal of symptoms and the presence of neuropathy, itching, and legs cramps — conditions also common in this group. Thus, the reliability of self-administered questionnaires to diagnose RLS in ESRD patients has typically been low.²¹³ Despite the problem of accurate diagnosis, however,

there appear to be racial and ethnic differences in the prevalence of RLS in the ESRD population. For example, RLS is less common in those of Indian²¹⁴ and African American descent²¹⁵ than those of European descent. For unknown reasons, ESRD patients also often experience more PLM than individuals with idiopathic RLS.²¹⁶ Both RLS and a PLM index greater than 20 are significant independent predictors of mortality in this population.²¹⁷ Quality of life is also adversely affected.^{218,219}

The causes of the high prevalence of RLS in ESRD remain to be fully described. Data regarding the clinical and laboratory correlates are limited and contain several inconsistencies. For example, in one study, higher predialysis urea and creatinine levels were associated with increased RLS complaints²⁰⁵ while in others no relationships between these variables were detected.^{206,210} Higher intact PTH (parathyroid hormone) levels have been found in dialysis patients with PLM versus those without the disorder²⁰⁹ but lower PTH levels were noted in ESRD patients with RLS in comparison to those without symptoms.²¹⁰ Anemia has been linked to RLS^{207,220} and normalization of hematocrit with recombinant erythropoietin has resulted in a significant reduction in PLM.¹⁰⁷

Treatments that may be effective for patients with ESRD and RLS include the intravenous administration of erythropoietin¹⁰⁷ and iron dextran²²¹ and the use of oral medications such as clonidine²²² and dopaminergic agents.^{166,223,224} Dopamine precursors, such as carbidopa/levodopa, are effective in managing RLS in this population, but possible rebound and augmentation should be carefully monitored.¹⁴⁹ Gabapentin is a treatment option²²⁵ but the dosage typically needs to be reduced for use in these patients and administered immediately after dialysis.²¹³ Opioids may be used intermittently and long-term if patients are followed closely for dependency, side effects of the medication, and the development of sleep apnea.^{105,213} Clonazepam has also been used to successfully treat RLS in this group⁷, an effect that may be more related to the drug's sedative properties than direct effects on RLS symptoms. Treatment should also include the reduction of potential exacerbating agents such as tricyclic antidepressants, selective serotonin uptake inhibitors, lithium, and dopamine antagonists.²¹³ The type of dialysis does not appear to influence the severity of symptoms,^{149,226} but one of the most effective treatments for RLS in ESRD is renal transplantation.^{74,75}

SECONDARY RLS (continued)

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.²²⁷ Supplementation with vitamins such as C, E,²²⁸ 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.^{229,230} 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.¹⁰⁶ 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.²³¹ 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 supplementation in treating RLS failed to find any significant difference in symptom improvement with treatment.²³² However, the patients had higher levels of ferritin than those in O'Keeffe's study,⁸¹ and no clinically significant improvements in the level of ferritin were seen after treatment. This underscores an important biological issue: patients with normal ferritin 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.²³³ 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 greater than 60 to 80 mcg/L, probably less than 2% of the non-heme iron is absorbed.²³⁴ 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.²³⁵ 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 three 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 two hours after meals. It should not be given with food, antacids, or calcium.

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.

CHILDREN AND RLS

Recent literature reveals that RLS occurs more frequently in children than previously recognized. Young children present a diagnostic challenge since many symptoms of RLS are subjective and difficult to explain, even for adults. A workshop at the National Institutes of Health in May 2002 resulted in specific consensus criteria for the diagnosis of pediatric RLS.¹⁹ (Table 6) Objective measures for RLS include recording PLMS; however, no studies to date have demonstrated normative values for PLMS or reliable recording standards for children. Participants and “experts” in the NIH-sponsored workshop on recognition and diagnosis of RLS therefore intentionally made it difficult to arrive at a definite RLS diagnosis in childhood. Probable and possible RLS categories were developed to promote research in this area. Over time, a more simplified and objective diagnostic scheme is expected.

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.”²³⁶⁻²³⁸ In others, the leg-jerking during sleep (PLMS) may be the key finding in diagnosis, with leg discomfort absent or very mild.²³⁹ Whether subjective sensory symptoms or objective motor symptoms predominate, there is usually a family history of similar symptoms which often go unrecognized until they appear in the children. 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.^{237,238,240-245} Further research is needed to understand the association of these disorders with RLS and PLMS, and to determine if there is a biological explanation for the occurrence of these problems in the same individual.

Diagnosis

Approximately 40% of adults with RLS report the onset of RLS prior to age 21.^{21,28,114} Unfortunately, the identification of RLS and PLMS in general pediatric populations is poor due to lack of knowledge about the disorder.²⁴⁶ In part, the lack of current knowledge in pediatrics reflects a preponderance of RLS studies focused primarily on adult populations.

In all categories, the importance of a family history of

Table 6 | 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

RLS and the occurrence of PLMS is acknowledged. Since RLS tends to respect an autosomal dominant mode of transmission, there is much to be gained from studying the phenotypic presentation and genetic predisposition of children in families with RLS. In order to use PLMS as a diagnostic criterion for RLS/PLMD in children, normative age-dependent standards need to be developed. In part, the lack of age-dependent norms may be related to the current standard of single night recording with polysomnography. Recent studies demonstrate that PLMS vary in children with and without RLS symptoms from night to night.²⁴⁷ Therefore, consideration of multi-night recordings may be important in the diagnostic work-up of children with symptoms suggestive of RLS.

Until recently, reference to childhood RLS and PLMS in the medical literature was infrequent and often incidental.^{244,245} However, more recent reports have documented multiple childhood and adolescent cases.^{205,237,239,241,242,248-253} An interesting association between RLS/PLMD and attention deficit/hyperactivity disorder (ADHD) has been demonstrated in multiple studies. Some

CHILDREN AND RLS (continued)

reports suggest that up to 40% of children presenting with symptoms of RLS/PLMD may also fulfill criteria for ADHD.^{238,240,243,354-256} The nature of this intriguing relationship is the topic of ongoing research. Another important element in the diagnostic work-up of children with RLS/PLMD symptoms is serum iron studies. Three studies of children and adolescents with RLS/PLMD have demonstrated a surprisingly high (up to 78%) incidence of iron deficiency in this population.^{252,253,257} The interrelationships between iron metabolism, RLS and ADHD has not been ferreted out, but is implied by the research, albeit limited, on RLS in childhood.

Treatment

There are similarly limited comprehensive investigations of treatment for RLS in the pediatric population (i.e., dopaminergic or benzodiazepine medications). Most “evidence” is gleaned from a few case reports and two case series of children with RLS and/or PLMD. The 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, pramipexole, ropinirole,²⁶⁷ and clonidine.^{237-239,249,258,192,253,259} In three studies where an association between childhood RLS/PLMD and iron deficiency was made (as determined by measurement of serum ferritin levels), therapy to correct the iron deficit was successful in relieving RLS symptoms in most subjects.^{252,253,257} As to safety in children, medications such as benzodiazepines,^{260,261} anticonvulsants,^{262,263} alpha-adrenergic agents,¹⁹² and opioids^{264,265} have been used extensively in children with disorders other than RLS, as has chronic use of levodopa for dopa-responsive dystonia.²⁶⁶ In a small open-label trial of dopaminergic medication used in six children with RLS and ADHD, an improvement was demonstrated in RLS symptoms and sleep, as well as in scores of attention and impulsivity.²⁴¹ In a study of children with PLMD, pramipexole was used in a subgroup and shown to be safe and effective.²⁵⁸ In association with any medical therapy for RLS it is implicit that interventions for behavioral, sleep schedule, and sleep hygiene related problems occur before or in coordination with the medical therapy.

For more information, please see the RLS Foundation’s *Children and RLS: Restless Legs Syndrome and Periodic Leg Movement Disorder in Children and Adolescents: A Guide for Healthcare Providers*.

Restless Legs Syndrome Foundation

The Restless Legs Syndrome (RLS) Foundation is a 501(c)(3) non-profit organization dedicated to increasing awareness, improving treatments, and through research, finding a cure for RLS. The RLS Foundation prides itself as being the preeminent source of unbiased, research-based and up-to-date information on this often devastating condition that affects millions.

The Foundation offers a Healthcare Provider membership which includes access to all publications for professionals and for patients, two issues per year of *The RLS Scientific Bulletin*, and many other benefits. Contact the RLS Foundation at 507-287-6465, at rlsfoundation@rls.org or at www.rls.org for more information or to become a member.

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