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Recognizing and Treating Restless Legs Syndrome: Current Standards

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Recognizing and Treating Restless Legs Syndrome: Current Standards

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Recognizing and Treating Restless Legs Syndrome: Current Standards

Statement of Need

Restless legs syndrome (RLS) is a common but poorly understood sensorimotor neurologic disorder likely to be encountered by primary care clinicians. The condition occurs in up to 15% of the general population and contributes to sleep disorders and a poor quality of life. Despite a growing recognition of RLS in clinical practice and effective available treatment, the condition remains underdiagnosed and undertreated. In fact, many patients remain undiagnosed for years after onset of symptoms, thus delaying or preventing effective treatment. Therefore, knowledge of and familiarity with the clinical presentation and diagnostic features of RLS will facilitate primary care clinicians’ ability to effectively treat patients.

Etiology and Pathogenesis

RLS is a complex disorder that may result from a complex dysfunction of interacting neuronal networks at one or several levels of the central nervous system and involve numerous neurotransmitter systems. The underlying causes of RLS remain unclear. RLS can occur as a primary disorder, with no apparent cause other than a possible genetic predisposition, or as a secondary condition, most commonly related to iron deficiency, pregnancy, or end-stage renal disease. Our current understanding of the pathophysiology suggests that RLS is related to abnormalities in the body’s use and storage of iron and to dopaminergic dysfunction.

Two potentially different phenotypes of RLS have been defined based on the presence of a family history and the age at symptom onset.

A family history of RLS is common among patients whose symptoms appear before age 45 years. These patients have a slower progression of RLS symptoms, a more common occurrence among first-degree relatives, and less of a relation between body iron stores serum ferritin and symptom severity. Patients with late-onset (>45 years of age) RLS may progress more rapidly, demonstrate a strong relation between symptom severity and low serum ferritin levels, and more often have a secondary form of RLS, including neuropathy.

Clinical Presentation

The prevalence of RLS in adults ranges between 5% and 15%. Prevalence increases with age and appears to be greater in women than in men. RLS presents with a variety of symptoms, including unpleasant sensations between the ankle and the knee, occasionally involving the whole lower limb. In more severe cases, the unpleasant sensation sometimes involves the upper limb. Typically, symptoms occur when the person is inactive, especially when trying to sleep. A key feature is that the unpleasant sensation compels the person to move. RLS may be confused with periodic limb movements of sleep (PLMS), which occur in a majority of patients with RLS. However, PLMS occur in other conditions that must be distinguished from RLS.

RLS severity ranges from merely annoying to symptoms that affect sleep and quality of life severely enough to require medical treatment. In a community-based study of RLS, 33.8% of all patients with RLS had mild, 44.6% had moderate, and 21.6% had severe disease; however, no patient had been previously diagnosed or was receiving dopaminergic therapy. In the large, multicountry RLS Epidemiology, Symptoms, and Treatment (REST) studies, which surveyed 23,000 patients from primary care physician practices, 9.6% of patients reported weekly RLS symptoms. Importantly, RLS was commonly undiagnosed and not appropriately treated.

Management

RLS is diagnosed on the basis of the patient’s history and clinical symptoms. Therefore, asking about and recognizing the signs and symptoms are crucial. Because misdiagnosis and delayed diagnosis are common, minimum criteria have been established by an international RLS study group to help achieve an early and accurate diagnosis. Current standards of practice for RLS limit therapy to individuals who meet specific diagnostic criteria. Thus, before deciding on a therapeutic approach, clinicians must make the correct diagnosis. Once the correct diagnosis has been made, the decision to treat is based on the disease severity and impact on the patient’s life. Before pharmacologic therapy is initiated, nonpharmacologic measures should be tried and secondary causes addressed.

Dopaminergic pharmacotherapy is the standard of treatment for RLS. Until recently, levodopa was the best-studied medication for RLS. However,
augmentation is a major complication that occurs after a period of time on levodopa therapy. Augmentation is present when RLS symptoms occur earlier in the day (when not at rest or asleep) and possibly emerge in the trunk or upper limbs. Evidence-based and clinical guidelines recommend newer dopamine agonists as first-line treatment for daily RLS symptoms. These agents are often used to minimize the chance of augmentation and potential for adverse drug effects. New agents are undergoing clinical trials and the process of registration for RLS. The first dopamine agonist was approved by the US Food and Drug Administration (FDA) in May 2005. When first-line agents fail or induce adverse effects, weak opioids, benzodiazepines, anticonvulsants or, if needed, strong opioids, may be used.

Conclusions

Media campaigns for new medications for RLS have focused a great deal of public attention on this condition. This media attention invigorated clinicians’ interest in the topic. In light of increasing knowledge about the pathophysiology of RLS and development of new effective therapeutic agents, clinicians must become more aware of RLS and more familiar with its diagnostic criteria to treat it optimally. Specifically, clinicians must be aware of the high prevalence of RLS, the potential for onset before age 20, and the various clinical presentations.

Recommendation

Although it has been frequently underrecognized, misdiagnosed, and undertreated in the past, significant advances in our current understanding of the epidemiology, clinical assessment, pathophysiology, and treatment of RLS have been made in the past year. To treat the condition appropriately, a high index of suspicion is required to make the diagnosis and start treatment quickly. Therefore, familiarity with diagnostic criteria and updated standards of care is essential for clinicians treating patients with RLS. For clinicians to render optimal care, educational programs about RLS are needed to keep physicians informed about the latest advances that can improve patient’s quality of life.

References


Program Overview

This CME supplement is derived from editorial teleconferences held in February and March 2006.

Target Audience

This activity is designed for clinicians treating patients with RLS: internal medicine and family practice physi-
cians, general practitioners, obstetricians/gynecologists, doctors of osteopathy, nurse practitioners, and physician assistants.

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Educational Objectives

Upon completion of this activity, participants should be able to:

- Discuss the etiology of primary and secondary RLS
- Diagnose RLS according to current standard criteria
- List currently available first-line and alternative treatments for RLS
- Develop an RLS management plan according to symptom severity and impact on the patient’s life

Method of Instruction

Participants should carefully review the entire activity, including the educational objectives, needs statement, target audience description and other material in this CME Information section. After review, read the text, and complete and submit answers to the posttest questions, credit claim verification of participation, and activity evaluation.

Participants must achieve a passing grade (≥70%) to receive credit. Nonphysicians will receive a certificate of participation. Please be sure to complete and sign the credit claim form to receive the appropriate credit.

There is no fee for participation. The estimated time to complete this self-study educational activity is approximately 2 hours.

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Introduction

Restless legs syndrome (RLS) is a sensorimotor neurologic disorder present in 5% to 10% of the US population, although only 25% of such individuals probably warrant regular treatment. It commonly causes sleep disturbance, which is often severe, and is the primary reason that patients present for treatment. Therefore, it is important for primary care physicians, who see the majority of patients with sleep problems and painful conditions, to understand the differential diagnosis of these symptoms, including RLS, and offer optimal treatment. It should also be noted that the diagnosis and management of RLS can be challenging for neurologists and sleep medicine specialists who do not treat such patients specifically. This supplement to The American Journal of Medicine is intended to present current information about the epidemiology, consequences, diagnosis, and treatment of RLS, as well as to provide a general approach to managing patients and determining when referral is appropriate.

HISTORICAL PERSPECTIVE

RLS has had a long history as a medical condition; it was first recognized >300 years ago. However, it is only recently that it has received substantial attention in the medical literature. For most of its history RLS was considered a nonspecific, possibly psychological, disorder. Symptoms were originally described by Willis (famous for the circle of Willis) in 1685 as “leapings and contractions of the tendons, and so great a restlessness and tossings of their members ensue that the diseased are no more able to sleep than if they were in a place of the greatest torture.” It was reintroduced to medicine 200 years later and described as the psychiatric disorder “anxietas tibiarum.” The hysterical etiology was largely accepted until 1945, when Ekbom provided a modern description of the organic features of the disorder and was the first to suggest the term “restless legs syndrome.” During the past 20 years, there has been a dramatic increase in our understanding of the epidemiology, risk factors, pathophysiology, clinical consequences, and treatment of RLS. To facilitate a reliable and valid diagnosis, minimal criteria were established at a National Institutes of Health (NIH)–sponsored consensus conference of international experts in sleep disorders, epidemiology, movement disorders, and nosology. These revised criteria reflect a set of symptoms that can be easily used by clinicians and researchers to recognize and diagnose RLS. As a result, recent epidemiologic studies have consistently found a 5% to 10% prevalence of RLS in northern European countries and in North America. Although Ekbom recognized that RLS was frequently a familial disorder, and that it could be associated with iron deficiency, recent research has more clearly identified potential chromosomal loci in familial RLS, as well as the importance of central nervous system iron abnormalities in this disorder. Modern treatment of RLS began with reports of the successful use of levodopa treatment. More recently, dopamine agonists have been used increasingly as medications of first choice. Currently, there are 2 medications (ropinirole and pramipexole) that are approved by the US Food and Drug Administration (FDA) for treatment of RLS.

RESTLESS LEGS SYNDROME AS A SLEEP DISORDER

By definition, symptoms of RLS occur when an individual is at rest; they become most prominent in the evening or at
night, when the individual is trying to sleep. Thus, although sleep complaints are not part of the diagnostic criteria, it is not surprising that RLS often has been considered a sleep disorder. In fact, sleep disturbance is considered by patients to be the most distressing aspect of RLS and appears to account for most of its morbidity.1,10 Sleep disturbances are also the primary reason that people seek medical attention for RLS.11,12

In the first article in this supplement, Dr. Clete A. Kushida discusses the presentation, diagnostic, and quality of life issues associated with RLS. Although RLS is among the most common causes of sleep disturbance, it remains largely undiagnosed in the primary care setting.13 Physicians give a wide range of diagnoses for RLS symptoms. In fact, recent studies suggest that although individuals with RLS often describe the symptoms to their physicians, only a minority (5% to 25%) of them are appropriately diagnosed.11,14 Unfortunately, there are no laboratory tests that can confirm the diagnosis. Therefore, it is essential that clinicians become familiar with the common clinical presentation of RLS. The old saying in medicine that “you can’t make the diagnosis unless you think of it” is apt in this regard. Recently published diagnostic criteria, single screening questions, and acronyms should help clinicians ask patients about, recognize, and diagnose RLS appropriately.

The importance of appropriate diagnosis and treatment is underscored by the substantial morbidity of untreated RLS. It can impair normal life functioning as a result of sleep disturbance, depression, fatigue, and avoidance of social, professional, or recreational activities. Because clinicians often fail to recognize RLS as a distinct disorder, they have tended to minimize the seriousness of the morbidity experienced by patients.13 Furthermore, even when diagnosed, RLS is often inappropriately treated, which may contribute to continued distress for patients.11

In his article, Dr. Richard P. Allen describes current controversies and challenges in determining the etiology and pathophysiology of RLS. At the present state of knowledge, the etiology and pathophysiology of RLS remain unclear. It may occur as a primary disorder in individuals with a genetic predisposition or it may manifest as a secondary condition, most commonly associated with iron deficiency. To date, 2 different phenotypes have been defined on the basis of the presence of a family history and the age at symptom onset.13

A central dopaminergic dysfunction associated with abnormalities in brain iron metabolism is postulated to be the major contributor to symptoms of RLS.15 However, the mechanism of these disturbances is unknown. Brain imaging, cerebrospinal fluid, and serum studies provide evidence of decreased brain iron in RLS. The efficacy of dopaminergic agents in RLS supports a hypothesis of dopaminergic dysfunction for this disorder; however, neuroimaging studies have been mixed, at best, in this regard. Understanding the pathophysiology of RLS may lead to better treatment approaches for those requiring treatment.

In the third article, Dr. Wayne A. Hening reviews current guidelines and standards of practice for the management of RLS. In 1999, the first evidence-based guidelines for RLS recognized that it was a serious sleep disorder and that it was important for practitioners to be familiar with RLS, to be able to diagnose the condition, and to provide appropriate management. Until 2004 most treatment standards concerned only dopaminergic agents. In 2004, an algorithm developed by the Medical Advisory Board of the RLS Foundation classified patients into 3 groups on the basis of severity of symptoms, and incorporated both nonpharmacologic and pharmacologic management. This algorithm matches therapy to disease severity (i.e., occasional symptoms, daily symptoms, refractory symptoms). Augmentation, which can become a problem with dopaminergic therapy, and the special needs of certain patient populations, including children and pregnant women, are also addressed. Most internists and family physicians can diagnose RLS and provide primary therapy. However, each physician must decide whether he or she wishes to get involved with more refractory patients who require complicated adjustments of medication. In those cases, referral to a recognized RLS expert is appropriate.

In the final article, I describe the need for improved diagnostic tools and further research, as well as the development of pharmacologic agents that may offer a better future for patients with RLS. Equipped with information about its clinical presentation, diagnostic criteria, and treatment approaches, clinicians in primary care practices will be in a better position to manage patients without referral to a specialist, and to determine when such a referral might be warranted.

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References

Clinical Presentation, Diagnosis, and Quality of Life Issues in Restless Legs Syndrome

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ABSTRACT

Restless legs syndrome (RLS) is a generally underdiagnosed and undertreated condition. It is a common cause of sleep disturbance that can severely disrupt normal life functioning. However, because of the failure to recognize RLS as a distinct disorder, clinicians have minimized the significance of the morbidity experienced by some patients. A positive family history is present in >50% of patients with RLS. Indeed, a person with RLS is 3 to 6 times more likely to have a positive family history of RLS than is an individual who does not have the disease. The differential diagnosis of RLS includes both movement and sleep disorders. Establishing an accurate diagnosis is crucial because effective treatment is available. In 2002, RLS experts revised diagnostic criteria and established 4 essential criteria for the diagnosis. Assessing the most bothersome symptoms and quantifying the severity of RLS are important because not all patients require medical therapy. Moreover, therapy may vary according to which symptom represents the major problem. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Diagnosis; Presentation; Quality of life; Restless legs syndrome

Restless legs syndrome (RLS) is a sensorimotor disorder typically characterized by an uncomfortable feeling in the legs that leads to an urge to move. A recent large multinational survey in the primary care population indicated that RLS is a common cause of sleep disruption that remains undiagnosed in the primary care setting. The same survey reported that physicians often gave a wide range of diagnoses for RLS symptoms, including varicose veins/venous problems, back/spinal problems, neuropathy, and depression. In fact, only approximately 25% of patients with RLS symptoms were appropriately diagnosed. Even when diagnosed, RLS is often inappropriately treated, and inappropriate treatment may contribute to continued distress for patients.

RLS can severely disrupt normal life functioning. However, because of the failure to recognize RLS as a distinct disorder, clinicians have minimized the significance of the morbidity experienced by some patients. Symptoms of RLS may be more prevalent in the primary care population compared with the general population. That is, a greater proportion of persons with RLS symptoms may visit their physicians than prevalence rates for symptoms in the general population would suggest. This could be because sleep deprivation associated with RLS may contribute to other problems for which the patient seeks treatment from a primary care physician. In addition, patients may also seek medical attention for the symptoms of RLS itself. However, in many instances, the RLS may not be adequately managed, as discussed in the study by Hening and colleagues.

Primary care clinicians are in a unique position to make the diagnosis and provide medical treatment for most patients with RLS. Therefore, it is essential that they become familiar with the clinical presentation, diagnostic criteria, and treatment options for RLS.

COMMON CLINICAL PRESENTATION

The diagnosis of RLS is largely based on the patient’s report of clinical symptoms, the most striking of which are the patient’s inability to remain at rest (the urge to move, mostly the legs)
and the marked discomfort the patient experiences when forced to stay at rest. Another important clinical feature is the circadian variation of symptoms, which are worse in the evening and at night. Allen and Earley\(^2\) reported 6 critical features that distinguish RLS from other disorders (Table 1).

When the diagnosis is uncertain, it is important to inquire about factors that alleviate or exacerbate the symptoms. For example, physical stimulation (e.g., rubbing the legs, walking) or intense, concentrated mental activity appear to reduce the symptoms. Factors that lead to reduced arousal (e.g., restricted or confined activity, drowsiness) tend to exacerbate or precipitate the symptoms. Patients often report problems when riding in a plane or car for long periods of time, when sitting during long meetings or performances, or when attempting to sleep.

The frequency and severity of the unpleasant sensations increase with the duration of rest. Relief from symptoms persists as long as the limb is in motion. However, because symptoms may recur as soon as movement stops, patients may not report any relief with movement. Therefore, clinicians should ask patients whether they experience relief during the movement itself.\(^2\) With severe RLS, it is sometimes the case that relief with movement may not occur and symptoms may be present 24 hours a day. However, the patient should be able to recall a period in the past when he or she obtained relief with movement and when symptoms were worse in the evening or at night.\(^4\)

Individuals often have difficulty describing the unpleasant sensations experienced with RLS. Some of the terms used include “creepy crawling,” “jittery,” “soda bubbling in the veins,” “shock-like feelings,” “worms moving,” “heebee-jeebies,” and “itching bones.” A common thread appears to be the sensation of movement deep within the leg rather than superficially or on the surface of the leg. For some patients, RLS symptoms may also involve other body parts, such as the arms. With increasing severity, symptoms may spread to the trunk and face. However, by definition, RLS must involve the legs.\(^4\)

### Obstacles to Recognizing and Diagnosing RLS

The RLS Epidemiology, Symptoms, and Treatment (REST) study was conducted in 2 populations. In the first study, conducted in 23,000 patients from primary care physician practices in 5 countries, only 24.9% of participants received a diagnosis of RLS.\(^1\) In the second REST study, conducted in a general population of \(>16,000\) patients (not strictly primary care patients, although a large proportion of patients sought medical help for RLS symptoms), only 6.2% received a diagnosis of RLS. Symptoms were attributed to better-recognized medical conditions such as back pain, arthritis, or peripheral neuropathy. The investigators proposed that the low diagnostic rate was owing to a lack of familiarity with the disorder and the fact that RLS is not generally recognized as a medically significant disorder.\(^5\) Diagnosis may be particularly challenging in the elderly, who tend to have a greater number of comorbid conditions that mimic symptoms of RLS. In addition, dementia and stroke may confound the accurate diagnosis of RLS in this population.\(^6\)

### Risk Factors for RLS

A positive family history is present in \(>50%\) of patients with RLS. Indeed, a person with RLS is 3 to 6 times more likely to have a positive family history of RLS than an individual who does not have the disease.\(^3\) Most epidemiologic studies indicate that the prevalence of RLS increases with age and is more prevalent in women than in men. However, Phillips and co-workers\(^7\) found that the prevalence of RLS increased with age but did not differ significantly by sex. They also found an association with lower annual income levels (<\$25,000), which may be related to the supposition that this subgroup generally has a higher frequency and severity of medical problems. RLS was more prevalent in smokers and in individuals who exercise \(<3\) hours each month. Last, individuals with diabetes mellitus were 4 times more likely to have RLS compared with their nondiabetic counterparts.\(^7\)

### Differential Diagnosis

The differential diagnosis of RLS includes both movement and sleep disorders.\(^8\) Table 2 lists conditions associated with the differential diagnosis.\(^2\) Most of these conditions

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Features distinguishing restless legs syndrome from other conditions</th>
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<tbody>
<tr>
<td>• Engendered at rest, unrelated to body position or other activity, occurs when resting or lying down</td>
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<tr>
<td>• Patient experiences an internal urge to move a body part, usually the limbs (not a spontaneous general body movement)</td>
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<tr>
<td>• Focal akathisia is relieved immediately (at least partially) by movement of the affected limb</td>
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<tr>
<td>• Relief with movement persists as long as the limb is being moved (symptoms may reoccur as soon as movement ceases)</td>
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<td>• There is usually a time of day when symptoms are not present or are less severe, typically a circadian pattern when symptoms appear at the end of the day or at bedtime</td>
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<tr>
<td>• There are no signs of disease in the affected limbs</td>
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Adapted from J Clin Neurophysiol.\(^2\)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Differential diagnosis of restless legs syndrome</th>
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</thead>
<tbody>
<tr>
<td>• Neuropathic pain syndromes</td>
<td></td>
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<tr>
<td>• Peripheral neuropathy</td>
<td></td>
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<tr>
<td>• Arthritis</td>
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<tr>
<td>• Nocturnal leg cramps</td>
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<tr>
<td>• Restless insomnia</td>
<td></td>
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<tr>
<td>• Painful legs and moving toes</td>
<td></td>
</tr>
<tr>
<td>• Vascular insufficiencies</td>
<td></td>
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<tr>
<td>• Drug-induced akathisia</td>
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Adapted from J Clin Neurophysiol.\(^2\)
typically do not have a circadian pattern, nor does movement relieve the symptoms. Furthermore, although persons with these conditions may change position to feel more comfortable, these conditions are not typically associated with an irresistible urge to move. “Restless insomnia” and “painful moving legs and toes” are rare disorders that do not involve an urge to move the limb. Drug-induced akathisia usually involves spontaneous movement of the whole body. Although leg cramps may often occur at night, they are usually localized to specific muscle groups, accompanied by muscle hardening or knotting that can be palpated, and are not easily relieved with movement. Arterial insufficiency usually worsens with movement and improves with rest. Venous insufficiency is usually accompanied by swollen legs and changes in skin color.2,8

Periodic limb movements. Periodic limb movements in sleep (PLMS) and periodic limb movement disorder (PLMD) merit special mention because RLS is often confused with them. Up to 85% of patients with RLS experience PLMS, usually involving the legs. PLMS are described as involuntary clonic-type movements of the lower extremities while sleeping that usually involve bilateral ankle dorsiflexion, knee flexion, and hip flexion. They typically last approximately 0.5 to 5 seconds and occur every 20 to 40 seconds. They may result in multiple arousals and can disrupt sleep.4

PLMD is defined as a clinically significant sleep disturbance with PLMS that cannot be accounted for by any other sleep disorder. For example, many patients have PLMS in the presence of upper airway resistance (i.e., sleep-related breathing disorders). Thus, identifying the cause of PLMS has reduced the actual prevalence of PLMD, and its usefulness as a separate diagnostic entity has been questioned.2

Quantification of PLMS is performed with polysomnography in a sleep laboratory. Although PLMS commonly occur in RLS, PLMS also occur in sleep recordings of many disorders related to dopamine abnormalities (e.g., narcolepsy, rapid eye movement sleep behavior disorder, and Parkinson disease) and are not specific to RLS. They can occur with obstructive sleep apnea, neurodegenerative diseases, spinal cord lesions, stroke, and treatment with antidepressants or neuroleptic agents.9 PLMD is diagnosed if polysomnography reveals that the criteria for the duration, interval, amplitude, and frequency of the PLMS are met and the patient has either a clinical sleep disturbance or complaint of daytime fatigue.

Patients with RLS also may have periodic limb movements while awake (PLMW), which are diagnostically similar to PLMS.10 PLMW increase with the duration of rest, and from morning to night. The rest effect becomes more pronounced at night.10 Clinicians should be aware that ≥15% of persons with RLS do not have marked PLMS. Many patients with insomnia and PLMS do not have RLS; moreover, 20% of normal subjects show marked PLMW on objective tests.4

Types and Clinical Course of RLS

RLS may be subclassified into 2 related types: early- versus late-onset and primary versus secondary RLS.

Early- versus late-onset. Family history and age at onset appear to differentiate 2 phenotypes of RLS. Early-onset RLS, in which symptoms occur before 45 years of age, has an autosomal dominant mode of inheritance. Patients with earlier- rather than later-onset RLS generally have much slower progression of symptoms with age, have milder symptoms, more commonly have a family history of occurrence among first-degree relatives, and tend to have less relation between body iron stores and severity of disease.2 People without a family history generally have a later onset of RLS symptoms (>45 years of age). In this group, symptoms progress more rapidly with advancing age. For this reason, the most severely affected individuals tend to be middle aged or elderly.11 It also appears that most cases of secondary RLS (described below) are of the late-onset type. However, the evidence for this is conflicting. Allen and Earley2 proposed that many late-onset RLS cases may not be secondary, but instead may represent a modified form with delayed expression or expression after an environmental trigger. They explained this, in part, on the basis of data from some monozygotic twins with RLS who showed marked variation in the age at symptom onset. These researchers warned that this could indicate problems relying on patients’ recall of symptom onset for diagnostic accuracy, especially when symptoms are mild. Furthermore, there may be some genetic element that contributes to the occurrence of late-onset or secondary RLS.2

Primary versus secondary. RLS can be divided into primary and secondary forms, which are generally related to the age of onset. Primary, or idiopathic, RLS refers to patients without associated conditions that may explain the symptoms. In primary RLS, symptoms may begin by the second decade.

Before making a diagnosis of primary RLS, the clinician must diagnose and correct any secondary causes of RLS.11 Well-documented secondary causes of RLS include pregnancy, end-stage renal disease (ESRD), and iron deficiency. RLS occurs more commonly in persons with these conditions; however, only approximately one third to one half of patients with these conditions develop RLS. Symptoms also resolve with resolution of the condition. For example, RLS occurs in approximately 20% of pregnant women, but symptoms usually resolve within 1 month after delivery. Successful kidney transplantation and treatment of iron deficiency anemia have also resulted in resolution of RLS symptoms. Interestingly, in patients with ESRD, RLS predicts increased mortality.2

Clinical course. Although RLS appears to be a chronic condition, little is known about the pattern of expression of mild or intermittent RLS because most patients with this subtype typically do not seek treatment. It is also unknown whether this group experiences periods of remission. The clinical course
varies according to the age of onset. For those with more severe disease who seek medical attention, the severity and frequency of exacerbations usually increase over time. For those with late-onset RLS, there generally is a more rapid development of symptoms. In patients with early-onset RLS, symptoms develop more insidiously over many years and may not become persistent until the patient is 40 to 60 years of age. Although secondary RLS appears to remit with correction of the secondary condition, there are no long-term studies that have followed these patients for recurrence.4

CURRENT STANDARDS OF DIAGNOSIS

Establishing an accurate diagnosis is crucial because effective treatment is available. In 2002, RLS experts attending a diagnostic workshop sponsored by the National Institutes of Health (NIH) updated and revised diagnostic criteria to reflect a better working interpretation to be used by clinicians. The workshop established 4 essential criteria for diagnosis: (1) an urge to move legs that is usually accompanied or caused by uncomfortable or unpleasant sensations in the legs; (2) an urge to move or unpleasant sensation that begins or worsens during periods of rest or inactivity; (3) an urge to move or unpleasant sensation that is partially or totally relieved by movement as long as activity continues; and (4) urge to move or unpleasant sensation that is worse in the evening or at night during the day or that only occurs during the evening or at night (Table 4).4 Supportive and associated features are not essential to the diagnosis but may help resolve uncertainty.4

Special Populations with RLS

Criteria for diagnosing RLS in special populations (i.e., children and cognitively impaired elderly) were also proposed during the NIH workshop (Table 4). Because of language dysfunction in cognitively impaired adults, newly revised criteria have been established that emphasize behavioral indicators of RLS.4

RLS was rarely identified in children until recently. Epidemiologic studies and surveys reporting that 43% of adults had symptom onset between the ages of 10 to 20 years drew attention to the fact that the disease may begin earlier than previously thought.15 Children may report symptoms differently than do adults,4 and clinical manifestations in children may differ from those in adults. Symptoms may be mistakenly attributed to insomnia or growing pains and may go unrecognized by parents and clinicians.12 As is the case with adults, symptoms in children may be more common with rest and at night and may be relieved with movement. As a result, children may continue to move or struggle to remain awake or they may become fidgety when seated.12

The differential diagnosis in children includes cramps, sore muscles from overuse, Osgood-Schlatter disease, chondromalacia, familial neuropathy, and nerve compression from remaining in an awkward position.7 In children, RLS can lead to nocturnal awakening, unrefreshing sleep, and sleep-onset insomnia. Symptoms of RLS have been associated with cognitive and behavioral changes and attention-deficit/hyperactivity disorder (ADHD). However, it has been difficult to correlate RLS symptoms with the development of ADHD.12 Children with RLS may be mistakenly diagnosed with ADHD owing to the difficulty in accurately diagnosing either of these conditions in children.

How Is the Diagnosis Confirmed?

Physical examination and laboratory testing. Medical, physical, and neurologic examinations in primary RLS generally are normal. In addition, there is no reliable objective test that confirms the diagnosis. Therefore, laboratory tests generally are not helpful in diagnosing primary RLS.13 Evoked potentials, nerve conduction tests, and muscle biopsies are neither sensitive nor specific enough to be used diagnostically.14 However, certain findings may support the diagnosis. Patients with late-onset RLS may have evidence of associated conditions such as a peripheral neuropathy or radiculopathy.

It also is important for physicians to evaluate patients for iron deficiency and ESRD, which are common secondary causes of RLS; presence of these conditions will alter the treatment approach. A low serum ferritin level (≤45 to 50 μg/L) has been associated with increased severity of RLS and may be associated with an increased risk for RLS. Evaluation of serum ferritin levels and percent iron saturation is strongly recommended as part of the medical evaluation of patients with symptoms of RLS.4

PLMS. The finding of PLMS may support the diagnosis. During objective testing, PLMS are scored only if they occur in a series of 4 consecutive movements lasting 0.5 to 5 seconds, have an amplitude of ≥25% of the toe dorsiflexion during calibration, and are separated by intervals of 4 to 90 seconds. In adults, an index (number of PLMS per hour of sleep) of >15 for the entire night is considered pathologic.4

SIT. Montplaisir and colleagues14 developed a standardized test, the Suggested Immobilization Test (SIT), to evaluate PLMW. The SIT is a 60-minute test that requires the patient to recline in bed at a 45-degree angle with eyes open and legs stretched out. The patient is instructed not to move or fall asleep. Leg activity is recorded while an electroencephalograph (EEG) is monitored to ensure the patient is awake.2 The SIT assesses both subjective leg discomfort and the severity of PLMW. When used at various times during the day, it evaluates symptoms under fixed resting conditions and also assesses the effect of rest on leg discomfort and PLMW. The finding of an increase in the number of PLMW with increasing duration of rest directly tests the diagnostic criterion of an increase in leg movement with rest.10

Documentation of PLMS on polysomnography or of PLMW on SIT supports a clinical diagnosis of RLS; however, these tests are neither specific nor sensitive enough to confirm the diagnosis of RLS. In fact, it appears that current clinical diagnostic criteria for RLS render a more accurate
diagnosis than does either SIT or PLMW. Allen and associates reported that PLMW increased with the duration of rest and from morning to night; the rest effect became more pronounced at night. The authors concluded that this increase may be a more sensitive measure of RLS severity than is the measure of total PLMW.

Actigraphy. Actigraphy is another objective test of increased lower limb movement. Motor activity is monitored with a small, portable, wristwatch-like device worn at the ankle; the actigraph estimates leg movements during sleep and wakefulness. Actigraphy scores generally correlate with PLMS on polysomnography, but, again, they are not specific for RLS.

### RLS Comorbidities

In a survey of primary care patients, Hening and colleagues reported that physicians diagnosed patients with RLS symptoms with a wide variety of medical conditions in the 12 months before the survey. Conditions diagnosed in >10%

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### Table 3 Criteria for diagnosis of restless legs syndrome

<table>
<thead>
<tr>
<th>Criteria Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Essential criteria            | 1. Urge to move legs usually accompanied or caused by uncomfortable or unpleasant sensations in the legs (urge to move may not be accompanied by uncomfortable sensations, and arms or other body parts may be involved)  
2. Urge to move or unpleasant sensation begins or worsens during periods of rest or inactivity  
3. Urge to move or unpleasant sensation partially or totally relieved by movement as long as activity continues  
4. Urge to move or unpleasant sensation worse in the evening or at night than during the day, or only occurs during the evening or at night. In very severe cases, worsening at night may not be noticeable but must have been previously present. |
| Supportive clinical features  | 1. Positive family history  
2. Response to dopaminergic therapy (>90%)  
3. Periodic limb movements (during wakefulness or sleep) |
| Associated features           | 1. Natural clinical course  
2. Sleep disturbance  
3. Medical or physical evaluation is generally normal |

Adapted from Sleep Med.

### Table 4 Criteria for diagnosis of restless legs syndrome (RLS) in special populations

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| Essential criteria for diagnosis of probable RLS in the cognitively impaired elderly | 1. Signs of leg discomfort (rubbing, kneading)  
2. Excessive motor activity in lower extremities (pacing, fidgeting, kicking, tossing and turning in bed, tapping)  
3. Signs of leg discomfort exclusively present or worsen during periods of rest or inactivity  
4. Signs of leg discomfort diminished with activity  
5. Criteria 1 and 2 occur only in the evening or at night or are worse at those times |
| Criteria for diagnosis of definite RLS in children | 1. Child meets all 4 essential criteria for adults* plus  
2. Child’s description in her/his own words is consistent with leg discomfort OR  
1. Child meets all 4 essential criteria for adults plus  
2. ≥2 of the following supportive criteria:  
   a. Sleep disturbance  
   b. Biologic parent or sibling with RLS  
   c. PSG-documented PLMS index ≥5/hr of sleep |

PLMS = periodic limb movements in sleep; PSG = polysomnography.

*Criteria for diagnosis in adults: (1) Urge to move legs usually accompanied or caused by uncomfortable or unpleasant sensations in the legs (urge to move may not be accompanied by uncomfortable sensations, and arms or other body parts may be involved); (2) urge to move or unpleasant sensation begins or worsens during periods of rest or inactivity; (3) urge to move or unpleasant sensation partially or totally relieved by movement as long as activity continues; and (4) urge to move or unpleasant sensation worse in the evening or at night than during the day or only occurs during the evening or at night. In very severe cases, worsening at night may not be noticeable but must have been previously present.

Adapted from Sleep Med.
of patients with RLS and in those who had symptoms at least weekly are shown in Table 5.

**Sleep disturbance.** Although it is unknown what percentage of patients with RLS experience sleep disturbances, clinically almost all patients who seek treatment for symptoms of RLS have disordered sleep. The sleep disturbance typically involves initiating and maintaining sleep. When severe, this represents the primary morbidity of RLS. The RLS comorbidities of decreased functional alertness and emotional distress in our sample of patients appear to be mostly secondary to the sleep disturbance associated with RLS.

**Depression.** Sleep disturbance, depression, and RLS are closely linked. Emerging data indicate that depressive symptoms occur more commonly in adults with RLS than in those without RLS. However, symptoms of RLS may be misdiagnosed as symptoms of depression, and vice versa. For example, people with RLS commonly complain of fatigue, disturbed sleep, and diminished concentration. These symptoms can be interpreted as symptoms of depression or as directly related to the sleep disorder associated with RLS.

Various studies of patients with RLS report elevated scores on validated depression scales. Hornyak and associates investigated the relation between RLS symptom severity, sleep disturbances, and depressive symptoms using the International RLS Study Group (IRLSSG) rating scale and the Beck Depression Inventory (BDI) in 100 patients with moderate-to-severe RLS. Patients scored highest on items of reduced sleep, lack of energy, work difficulty, and indicators of physical symptoms of depression on the BDI. On the Pittsburgh Sleep Quality Index (PSQI), patients estimated their sleep quality as slightly-to-moderately impaired. The highest scores were in difficulties falling asleep or maintaining sleep. The severity of RLS was correlated with sleep quality and impaired sleep but not with self-reported depression symptoms. However, a higher degree of sleep impairment was correlated with higher depression scores.

The authors pointed out that the complex relation between depression, insomnia, and sleep disturbance confounds the relation between depression and RLS. The comorbidity simply may reflect an association of both disorders, or there may be a genuine comorbidity based on a common pathway involving the dopaminergic system. Finally, RLS may be associated with only a certain spectrum of depressive symptoms (somatic but not cognitive). Longitudinal studies exploring the relation between RLS and depression might further define the relationship.

Winkelman and coworkers examined the rates of depression and anxiety disorders in patients with RLS. Compared with controls, patients with RLS reported higher 12-month rates of depressive disorders, panic attacks, panic disorders, and generalized anxiety disorder based on standardized diagnostic criteria. Patients with RLS were more likely than controls to present with comorbid anxiety and depression. However, patients with RLS and depression attributed their depressive symptoms (especially sleep disorder) entirely to RLS.

The apparent comorbidity of RLS and depression underscores the importance of accurate diagnosis and treatment. An accurate diagnosis must include diagnosis of all comorbid conditions, and patients diagnosed with RLS should also be assessed for related mood disorders.

**Neuropathies/radiculopathies.** Neuropathies and radiculopathies have been associated with RLS. However, the relationship is complicated and the degree of the association between neuropathy and RLS is not known. Neuropathy occurs more frequently in individuals with nonfamilial RLS, may involve sensory symptoms, and presents at a later age. Using skin biopsy as a diagnostic tool to identify small-fiber neuropathy in patients with RLS complaining of sensory dysesthesias, Polydefkis and coworkers reported a late age of symptom onset in 80% of patients with abnormal skin biopsies compared with only 18% of patients who had normal skin biopsies. There also are case reports linking RLS to other conditions that present with neuropathy (e.g., cryoglobulinemic neuropathy, type 2 Charcot-Marie-Tooth disease, and familial amyloid polyneuropathy). In addition, neuropathy associated with rheumatoid arthritis and diabetes appears to occur more often in patients with RLS.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients with RLS, % (n = 551)</th>
<th>Other Patients with At Least Once-Weekly Symptoms, % (n = 1,006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>34.8</td>
<td>28.8</td>
</tr>
<tr>
<td>Depressed mood/depression</td>
<td>26.9</td>
<td>16.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26.1</td>
<td>24.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>26.0</td>
<td>16.5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>23.2</td>
<td>20.2</td>
</tr>
<tr>
<td>Arthritis</td>
<td>21.8</td>
<td>15.1</td>
</tr>
<tr>
<td>Nocturnal cramps</td>
<td>19.8</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Adapted from *Sleep Med.*

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Table 5: Conditions commonly diagnosed in patients with restless legs syndrome (RLS)
Assessing the Severity of RLS

Assessing the most bothersome symptoms and quantifying the severity of RLS are important because not all patients require medical therapy. Furthermore, therapy may vary according to which symptom is the major problem.

Two validated scales are used to quantify RLS symptom severity.2 One was developed by the IRLSSG. It is a 10-question scale; the questionnaire typically is completed by a person trained in administering the scale, who records the patient’s responses during an interview. The scale is divided into 5 questions that ask about symptom frequency and intensity, and 5 questions that address the impact of symptoms on daily life and sleeping. Each item is rated on a 5-point scale; higher scores represent greater RLS severity.2 The other scale was developed by the Johns Hopkins RLS Research Group. It focuses on the circadian characteristics, or the time of onset of symptoms. It is easier to use and has only 4 ratings (from 0 = none to 3 = severe). A 0 score means the patient has no symptoms. A score of 3 means the symptoms begin in early afternoon or may be present all day.2

Augmentation

Augmentation is characterized by increasing intensity of symptoms, earlier onset of symptoms in the day, reduced time at rest before symptoms start, and, occasionally, spread of symptoms to other body parts.2 Augmentation has been associated with use of older agents, such as daily doses of >2 tablets of carbidopa 25 mg/levodopa 100 mg. Augmentation represents the major complication of dopamine therapy for RLS.21 The prevalence of augmentation varies with the medication. It has been reported in up to 82% of patients taking levodopa and in up to 27% of patients taking pergolide. In terms of newer dopamine receptor agonists, Winkelman and Johnston22 reported that augmentation occurred in 32% of patients taking pramipexole. There are some anecdotal reports on augmentation with ropinirole, but no published data are yet available. A recent review suggests “careful tailoring” of the dopaminergic dose to avoid augmentation.23 Augmentation typically appears within 6 months after treatment begins and may be mild or severe. However, its occurrence does not indicate an increase in the severity of RLS itself.4

The NIH expert workshop that convened in 2002 proposed diagnostic criteria for augmentation (Table 6).4 By definition, symptoms occur ≥2 hours earlier than the usual time. No other medical, psychiatric, behavioral, or pharmacologic factor explains the exacerbation. Symptoms should be present for ≥5 days per week for ≥1 week.4

Clinicians should remember several conditions that mimic augmentation and that should be excluded when assessing patients. They include the natural progression of RLS, temporary worsening due to other factors such as sleep deprivation, iron deficiency, use of medications such as dopamine receptor antagonists or antidepressants, tolerance to therapy, and end-of-dose rebound.4 Ondo and associates24 reported that patients with nonfamilial and neuropathic RLS are less likely to develop augmentation.

Table 6 Key features of augmentation

- Increased overall intensity of symptoms temporally related to increase in daily medication
- Decreased overall intensity of symptoms temporally related to decrease in daily medications
- Latency of RLS at rest shorter than latency with initial therapeutic response
- Urge to move extended to previously unaffected limbs or body part
- Duration of treatment effect shorter than duration with initial therapeutic response
- PLMW occur for first time or worse than initial therapeutic response

PLMW = periodic limb movements while awake; RLS = restless legs syndrome.
Adapted from Sleep Med.4

Clinically, it is important to warn patients not to increase the dose of levodopa if RLS worsens. Also, an increase in symptoms due to augmentation should be distinguished from rebound (the recurrence of symptoms in the early morning when the drug wears off).25

Quality of Life Issues

The primary morbidities from RLS include sleep loss, extreme discomfort, and disruption of normal activities.26 Chronic sleep disruption and the inability to tolerate sedentary activities affect job performance, job tenure, the ability to enjoy life, and the quality of interpersonal relationships.27 In addition to the negative impact of RLS on daily functioning, a number of the agents used to treat RLS, including dopaminergic drugs and opiates, are associated with side effects.28 Thus, both the condition and the treatment can affect the patient’s quality of life (QOL).

Objective measures of QOL. The Restless Legs Syndrome Quality of Life (RLSQoL) questionnaire was developed to measure QOL issues specific to RLS.28 This 18-item questionnaire addresses questions such as how RLS affects daily activities, morning and evening activities, concentration, sexual activity, and work, all of which are assessed for the previous 4 weeks.26 Lower scores indicate lower QOL.26 Because it is specific to RLS and only takes 10 minutes to administer, this questionnaire is a valuable tool for clinicians.28 In a study by Abetz and associates,28 the RLSQoL overall impact scores distinguished between mild, moderate, and severe sleep problems. People with more severe sleep problems had statistically significantly lower scores (P <0.0001) and poorer QOL. Impaired QOL due to RLS was greater for patients with worse clinician-rated RLS severity (worse Clinical Global Impression of Severity [CGI-S] scores).28 A separate validated scale, the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI), has also been developed to measure RLS-specific QOL.27
had twice-weekly symptoms, and 2.4% of those surveyed reported an appreciable negative impact on QOL. Overall, 36.3% of participants reported that RLS symptoms had a highly negative impact on their lives. Symptoms appeared to have the greatest impact on sleep: 88.4% of participants had ≥1 sleep-related symptom (e.g., inability to fall asleep, inability to stay asleep, or disturbed sleep), and 43.4% rated sleep disturbance as their most troublesome symptom.\(^1\)

**Impact of RLS in the general population.** The second REST study characterized the clinical impact of RLS in a general population in which the symptoms were sufficiently frequent and distressing to warrant treatment.\(^5\) In this study, 85% of individuals surveyed reported that RLS symptoms disturbed ≥1 specific aspect of daytime functioning (Table 7).\(^5\) The most commonly reported problems were negative influence on mood (50.5%), lack of energy (47.6%), and disturbance of normal activities (40.1%).\(^5\)

Based on the Medical Outcomes Study Short Form-36 (SF-36), the reduced QOL in patients with RLS was comparable to that experienced by patients who had other serious medical conditions, such as diabetes and clinical depression.\(^5\) In addition, compared with normal controls, patients with RLS symptoms had a significantly higher rate of consultation with primary care physicians and specialists. Among 416 patients with RLS, 81% reported discussing symptoms with a physician. Of these individuals, 74.8% received some diagnosis, but only 6.2% received a diagnosis of RLS. Inappropriate diagnosis and treatment of RLS increases the patient’s suffering and contributes to excess costs of evaluation and adverse effects of treatment given for conditions mistakenly identified as RLS.\(^5\)

In the first REST study, conducted in a primary care population involving ≥23,000 participants, 11.1% of patients had symptoms of RLS and 9.6% had symptoms at least once a week (Table 8).\(^1\) An estimated 3.9% of patients had twice-weekly symptoms, and 2.4% of those surveyed reported an appreciable negative impact on QOL. Overall, 36.3% of participants reported that RLS symptoms had a highly negative impact on their lives. Symptoms appeared to have the greatest impact on sleep: 88.4% of participants had ≥1 sleep-related symptom (e.g., inability to fall asleep, inability to stay asleep, or disturbed sleep), and 43.4% rated sleep disturbance as their most troublesome symptom.\(^1\)

**Sleep disturbance.** Sleep efficiency is defined as total sleep time divided by the time in bed (i.e., time from lights out to begin sleep to time to leave bed to start the day).\(^2,26\) In a study in 26 patients with RLS, sleep efficiency averaged approximately 50%; 20% of patients had <3 hours sleep.\(^26\) Furthermore, RLS morbidity may be particularly marked in the elderly, in whom sleep is often compromised by other conditions that affect sleep.\(^2,26\) Severely affected patients with RLS may sleep less than patients with other major sleep disorders. Typically, patients with RLS do not report excessive daytime sleepiness, but they do feel tired and not fully alert.\(^2\)

**Depression and cognitive dysfunction.** In the Memory in Augsburg Elderly (MEMO) Study, depression was significantly more common among individuals with RLS compared with normal individuals.\(^29\) One study using polysonmography and EEG mapping assessed daytime brain functioning. EEG mapping of patients with RLS showed neurophysiologic correlates of depression, which were confirmed clinically by self-rating depression scales. Compared with control subjects, patients with RLS had significantly higher depression scores (P <0.001) and anxiety scores (P <0.01).\(^30\)

Phillips and coworkers\(^7\) found that RLS was significantly related to diminished general health and poor mental health as determined on the basis of patient self-report. Patients with RLS were 2.4 times more likely to report diminished general health than were those without RLS.

Kushida and colleagues\(^16\) examined the causal relation between the symptoms of RLS and specific health-related QOL consequences. These investigators concluded that the effects of sensorimotor manifestations of RLS on emotional and alertness functioning appeared to be moderated primarily through their impact on sleep disturbance (proportion of time kept awake, awakened from sleep, and prevented from falling back to sleep).

Although sleep loss is a major problem for patients with RLS, these individuals tend not to complain of sleepiness but do experience cognitive impairment. Using results from 6 different cognitive tests, Pearson and associates\(^31\) reported on findings of cognitive deficits in 16 untreated subjects with diagnosed RLS compared with normal controls. Subjects showed decreased performance on the Trail Making Test (TMT) and on a verbal fluency test, both of which focused on prefrontal cortex activity and were sensitive to sleep deprivation. Sleep efficiency correlated significantly with verbal fluency (fewer words were given with lower sleep efficiency).\(^31\) The authors concluded that untreated

### Table 7  Clinical impact of restless legs syndrome (RLS): The RLS Epidemiology, Symptoms, and Treatment (REST) study

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients Reporting Symptom (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory symptoms</td>
<td>88.0</td>
</tr>
<tr>
<td>Sleep-related symptoms</td>
<td>75.5</td>
</tr>
<tr>
<td>Disturbed daytime functioning</td>
<td>55.5</td>
</tr>
<tr>
<td>Symptoms affecting movement</td>
<td>37.0</td>
</tr>
<tr>
<td>Mood disturbance</td>
<td>26.2</td>
</tr>
</tbody>
</table>

Adapted from Arch Intern Med.\(^5\)

### Table 8  Impact of restless legs syndrome (RLS) symptoms in the primary care setting

<table>
<thead>
<tr>
<th>Symptoms Described by Participants</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 min to get to sleep (generally regarded as pathologic)</td>
<td>68.6</td>
</tr>
<tr>
<td>Waking ≥3 times per night</td>
<td>60.1</td>
</tr>
<tr>
<td>Lack of energy when experiencing RLS symptoms</td>
<td>60.8</td>
</tr>
<tr>
<td>Difficulty relaxing or sitting</td>
<td>60.1</td>
</tr>
<tr>
<td>Disturbed daily activities</td>
<td>57.2</td>
</tr>
<tr>
<td>Tendency to become depressed or &quot;low&quot;</td>
<td>53.9</td>
</tr>
<tr>
<td>Adverse effect on concentration</td>
<td>49.7</td>
</tr>
</tbody>
</table>

Adapted from Sleep Med.\(^1\)
individuals with RLS had statistically significant cognitive deficits similar to those seen in normal subjects who experienced 36 hours of total sleep deprivation. It is possible that the deficits might be a result of sleep deprivation rather than a direct effect of RLS pathology.

SUMMARY: WHAT SHOULD CLINICIANS KNOW ABOUT THE DIAGNOSIS OF RESTLESS LEGS SYNDROME?

RLS is underdiagnosed and undertreated. Although there are no reliable, objective tests to diagnose this condition, a diagnosis can be rapidly and accurately established in a physician’s office through careful evaluation of the patient’s symptoms. The primary morbidity associated with RLS appears to be related to sleep disturbance. Therefore, RLS should be considered in the differential diagnosis of any patient with sleep problems that involve a long latency and frequent awakenings. Clinicians should become aware of the presentation of late-onset and early-onset symptoms and recognize the most common secondary causes of RLS (i.e., iron deficiency, ESRD, and pregnancy). Familiarity with current diagnostic criteria is essential for effective RLS diagnosis. Furthermore, experts agree that rates of diagnosis could be improved by making the diagnostic criteria more widely known.

Recognition of primary and secondary RLS can reduce the burden of disease. Treatment of secondary causes often results in a resolution of symptoms. Effective treatment for RLS symptoms is available. Not all patients require therapy; therefore, management approaches should address symptoms on the basis of their severity and their bothersomeness to patients. Appropriate treatments will reduce the impaired QOL that the majority of RLS patients report.

References

Controversies and Challenges in Defining the Etiology and Pathophysiology of Restless Legs Syndrome

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ABSTRACT

Restless legs syndrome (RLS) can occur as a primary disorder, with no apparent cause other than a possible genetic predisposition, or as a secondary condition, most commonly related to iron deficiency, pregnancy, or end-stage renal disease. Recent studies have identified 2 different phenotypes of RLS based on age at onset of symptoms. Persons whose RLS symptoms start at an earlier age (<45 years) are more likely to have a family history of RLS and tend to have a more slowly progressive development of the disorder compared with individuals who have later onset of symptoms. In the past, our ability to determine either prevalence or population factors associated with increased occurrence of RLS has been limited. However, 4 different diagnostic criteria have been established. Familiarity with diagnostic criteria and clinical characteristics are essential for diagnosis and appropriate treatment, if required. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Dopamine; Epidemiology; Iron; Restless Legs Syndrome

Restless legs syndrome (RLS) is increasingly recognized as a common neurologic and sleep-related disorder that probably has multiple causes. Recent studies have identified 2 different phenotypes of RLS, early- and late-onset. Persons whose RLS symptoms start at an earlier age (<45 years) are more likely to have a family history of RLS and tend to have more slowly progressive development of the disorder compared with individuals who have later onset of symptoms. It seems likely that the pathophysiology differs for these 2 phenotypes. Recognizing this possibility has permitted more focused research, emphasizing the earlier-onset form of the disorder.

The original focus of research into RLS pathophysiology was driven by pharmacologic data supporting a possible dopaminergic abnormality, but the initial scientific studies failed to find convincing evidence for this contention. Clinical indications for an iron metabolic disorder have now been well established by replicated studies from different laboratories. The discovery of iron pathology in RLS provides a major and promising scientific approach to the study of RLS. Exploring this pathology may increase our understanding of the neurobiology producing RLS symptoms. In particular, this approach can be used to determine the iron-dopamine connection, thereby indicating possible dopamine abnormalities to be found in RLS.

Recent developments in clarifying the pathophysiology and epidemiology of RLS provide 2 important benefits. First, they open the door for finding better diagnostic and treatment approaches. It is even possible that some biologic marker for the disorder will be developed. Second, these recent developments dispel the myth that RLS is not a real disease but rather a fabrication designed to serve commercial interests. As discussed below, we now have excellent tools for the diagnosis of RLS, as well as the ability to conduct epidemiologic studies to establish a clear clinical picture of the disorder along with its prevalence and morbidity. More importantly, we now know more about the pathophysiology of RLS than we do about such conditions as chronic fatigue syndrome, fibromyalgia, or depression. These developments allow more accurate diagnosis and appropriate treatment of RLS and a better appreciation of its

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morbidity. Even when diagnosed in the past, RLS has often been inappropriately treated.4

PREVALENCE

Difficulties in Estimating Prevalence

In the past, 4 major problems have limited our ability to determine either prevalence or population factors associated with increased occurrence of RLS. First, the full set of 4 diagnostic criteria, as clearly specified in a National Institutes of Health (NIH) consensus workshop,5 was not used in most of the early studies. Any study not using the full criteria simply cannot be considered valid. No single question can possibly encompass all 4 criteria without being so complex as to create undue confusion. Thus, any survey with only 1 question cannot be considered valid.

Second, until recently we have not had a validated set of questions to use for estimating prevalence of RLS based on the 4 diagnostic criteria. We now have 2 such sets of questions. One validated set was used in the RLS Epidemiology, Symptoms, and Treatment (REST) studies4,5; the other was used in studies by Rothdach et al6 and Berger et al.7 These validated questions are described in detail below because they provide the best estimates of RLS prevalence.

Third, population-based studies need to include a differential diagnosis that excludes common conditions whose symptoms, at least on a questionnaire, may meet the 4 diagnostic criteria for RLS. These conditions include leg cramps, positional discomfort, and certain chronic pain conditions, including some neuropathies. With the exception of the REST studies (discussed below), the differential diagnosis problem has been largely ignored in epidemiologic investigations of RLS prevalence.4,5

The fourth problem is of a more technical nature. When a condition is relatively uncommon, for instance occurring in only 10% of the population, even a fairly specific and sensitive diagnostic questionnaire may have a very poor positive predictive value. For example, when a condition’s prevalence is 10%, an exceptionally good diagnostic questionnaire with both 90% specificity and 90% sensitivity has a positive predictive value of only about 50%. That is, half of the diagnosed cases do not have the disorder. With prevalence estimates, cases that are not diagnosed may partly compensate for the discrepancy. However, for population risk factors the problem may be more significant, particularly if the risk factors are such that they may distort symptom reports.

Despite these problems, the 4 epidemiologic studies that use the full diagnostic criteria with validated questions have produced remarkably similar results for certain North American and European populations. Rothdach and colleagues6 reported on a German population-based study in elderly patients (aged 65 to 83 years), whose RLS-trained physicians asked them about the following issues: (1) the presence of unpleasant sensations in the legs; (2) whether symptoms occur at rest and improve with activity; and (3) whether symptoms were worse in the evening or at night. Patients were only classified as having RLS if they responded “yes” to all 3 questions, and these questions were validated against an independent expert clinical evaluation. In this elderly population the overall prevalence rate was 9.76%, with higher prevalence in women than in men (13.9% vs 6.1%, respectively).5

Using the same set of diagnostic questions, Berger and coworkers7 found an RLS prevalence rate of 10.6% in a general population study of adults (aged 20 to 79 years) in northeastern Germany (Pomerania).7 Prevalence increased with age and, again, was about twice as common in women as in men. This group reported the interesting finding that prevalence rate for RLS in nulliparous women was the same as for men, suggesting the increased risk for RLS in women results at least partly from pregnancy.

The REST study was conducted in 2 populations using a diagnostic questionnaire.4,8 Both surveys used 4 questions based on the published international diagnostic criteria for RLS, which have been validated against an independent expert clinical diagnosis in a primary care population.9 The studies also included questions related to the differential diagnosis for excluding symptoms that are common mimics, thereby improving the specificity and positive predictive value of the results. More importantly, the REST study recognized the wide range of RLS symptom severity. The authors established guidelines for what they considered RLS of sufficient severity to require treatment (i.e., RLS occurring at least twice a week and reported to be moderately-to-severely disturbing).

The first REST study surveyed 23,000 patients from primary care physician practices in 5 countries. The prevalence rate was 11.1% for any degree of symptoms, and 9.6% of patients reported weekly RLS symptoms. The prevalence rate of clinically significant RLS was 2.7% in the primary care population.4

The second REST study surveyed a general population of >15,000 subjects. In this study, symptoms of any frequency occurred in 7.2% of the population surveyed; 5% had at least weekly symptoms, and 2.7% had symptoms at least twice weekly that were moderately or severely distressing.8

In both REST studies there were twice as many women as men for any level of RLS frequency or severity. The general population study showed that this gender gap was less pronounced for younger subjects (Figure 1).8 These studies were conducted primarily in persons of white European ancestry. Few data exist for other ethnic groups, such as African Americans or Asians, and none of these studies meet the criteria for an adequate population-based study using validated questions covering all of the basic diagnostic criteria. Moreover, there has been little effort to understand possible cultural differences in description of the diagnostic symptoms of RLS. Thus, at this point, we can say very little about prevalence in populations other than specific groups in North America and Europe.
Figure 1  Age distribution and prevalence of patients with restless legs syndrome (RLS) in the international RLS Epidemiology, Symptoms, and Treatment (REST) study population. (A) Age distribution of the survey population compared with international norms. (B) Prevalence of patients with RLS by age and sex. (C) Age distribution of the group of patients with RLS compared with the remainder of the population. (Reprinted with permission from Arch Intern Med.)
The only population-based study in a different ethnic group that clearly used all 4 diagnostic criteria was limited by asking only about symptoms that had occurred in the past 2 months. This study, from Turkey, found an overall prevalence rate of 3%. The mean age of patients with RLS was 43.3 years. The prevalence rate for women was 3.9%, whereas for men it was 2.45%.10

WHAT ARE THE SIGNIFICANT PHENOTYPES FOR RESTLESS LEGS SYNDROME?

As mentioned previously, 2 potentially different phenotypes of RLS have been defined on the basis of age at symptom onset.5,11 Differences in these phenotypes suggest that the etiology of RLS may differ in the 2 groups (Table 1).1,5,10–12 A complete description of these phenotypes is given in the article by Kushida13 elsewhere in this supplement.

Allen and Earley1 found that lower body iron stores, as measured by serum ferritin in patients with late-onset RLS, correlated significantly with greater severity (P = 0.02) based on the Johns Hopkins RLS severity scale (JHRLSS) and poorer sleep efficiency (P = 0.04). Thus, body iron, and not just brain iron, status is particularly important for late-onset RLS. Patients with late-onset RLS should be considered as having a complicated mixture of secondary RLS and primary RLS with symptoms exacerbated by secondary factors.

In patients with early-onset RLS, advancing age was correlated with increasing severity. In this group, JHRLSS scores increased with age from 45 to 80 years, whereas scores did not increase in a comparator group of patients with late-onset symptoms (Figure 2). Severity scores of those in the late-onset group were high initially and were comparable to the highest scores observed in those with early-onset RLS.1

The incremental increase in disease severity with age for patients with early-onset, but not late-onset, RLS is consistent with the slow progression of symptoms present only in early-onset RLS.1 The difference in the rate of development of RLS marks a clear difference in the pathologic processes associated with development of the condition. In this analysis of the different phenotypes, the group with early-onset RLS included many more persons with familial RLS (i.e., patients with close relatives who have RLS), whereas the late-onset group included more individuals with sporadic RLS (i.e., no first-degree relatives with RLS).1

Family Studies and Genetics

Compared with the general population, the risk for RLS is 7 times greater for the first-degree relative of a person with early-onset RLS and 3 times greater for a first-degree relative of a person with late-onset RLS.14 Segregation analyses have indicated that early-onset, but not late-onset, RLS is likely to have a significant genetic factor.15 Researchers have identified major genetic susceptibility loci for RLS on chromosomes 12q22-23,16 14q13-21,17 and 9p24-22.18 These studies, overall, suggest that RLS susceptibility likely has a polygenic explanation, although the possibility of a monogenic cause cannot be ruled out. It is expected, however, that a complex interactions of genes, gene modifiers, and environmental factors contribute to the development of RLS.

DEFINING THE PATHOPHYSIOLOGY

Genetic and family studies, brain imaging and cerebrospinal fluid (CSF) studies, similarities in secondary causes of RLS, and responses to pharmacologic therapy (dopamine agonists and antagonists) have all contributed to our knowledge about RLS.19 RLS can occur as a primary disorder, with no apparent cause other than a possible genetic predisposition, or as a secondary condition, most commonly related to iron deficiency, pregnancy, or end-stage renal disease (ESRD).5 All of these secondary causes share a common factor of compromised iron status, supporting the concept that iron pathology is a major contributor to the development of RLS. As mentioned previously, our current understanding of its pathophysiology suggests that RLS is related to abnormalities in the body’s use and storage of iron and, given the medication response, may also include a dopaminergic abnormality.4,20,21

The following 3 approaches have been used to define the pathophysiology of RLS: (1) studies attempting to localize the areas of abnormal central nervous system (CNS) function (e.g., spinal, cortical, subcortical areas); (2) studies of the neurotransmitter systems associated with medications that relieve the symptoms (dopaminergic); and (3) studies of the relation between iron deficiency and RLS.11 Laboratory evidence supporting abnormalities in dopamine and iron stores comes from studies of CNS and peripheral iron status and from brain imaging studies evaluating dopamine2 (D2) receptor ligand binding and brain iron stores. Clinical evidence suggesting RLS is associated with decreased dopaminergic neurotransmission includes the observation that RLS symptoms are worse at night when dopamine levels fall.22 Also, RLS improves with use of dopaminergic medications and is exacerbated with use of dopamine blockers.19 In addition, iron supplementation im-

Table 1 Early-onset versus late-onset restless legs syndrome (RLS)

<table>
<thead>
<tr>
<th>Early Onset</th>
<th>Late Onset</th>
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<tr>
<td>Symptoms appear before age 45 yr</td>
<td>Symptoms may progress more rapidly</td>
</tr>
<tr>
<td>Family history of RLS</td>
<td>More often a secondary form of RLS</td>
</tr>
<tr>
<td>Common among 1st-degree relatives</td>
<td>Neuropathy more common</td>
</tr>
<tr>
<td>Slower progression of symptoms</td>
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Adapted from Sleep Med,1,5 J Clin Neurophysiol,11 and Drugs Aging.12
Localizing the CNS Dysfunction

Localizing the anatomic areas of dysfunction for RLS has proved somewhat difficult, perhaps in part because this is a disorder with both sensory and motor dysfunction. Responses to medication for the treatment of RLS (specifically those that cross the blood-brain barrier) indicate that RLS results from abnormal functioning in the CNS, not the peripheral nervous system. For example, the dopamine antagonist metoclopramide, which crosses the blood-brain barrier, exacerbates symptoms of RLS. By contrast, domperidone, a dopamine antagonist that does not cross the blood-brain barrier, does not lead to the development of RLS symptoms. Thus, RLS dysfunction appears to involve the CNS. However, the specific areas involved are still being investigated.11

Recent interest and research has focused on impairment of subcortical inhibition in RLS. Electrophysiologic and transcranial magnetic resonance imaging (MRI) studies show increased cortical excitability and decreased subcortical inhibition, suggesting that the locus of the problem is subcortical, not cortical or spinal. Thus, looking at the specific neurologic systems in those regions may help define the primary pathology of RLS.11

Bara-Jimenez and colleagues24 tested spinal flexor reflex excitability in patients with RLS and periodic limb movements (PLM) at night during sleep (PLMS) and waking. RLS patients showed increased excitability during sleep compared with waking in contrast to the decreased excitability in control subjects.24 This state-dependent finding suggests that patients with RLS may have a reversal of normal sleep- or circadian-related spinal cord inhibition.11

High-resolution functional MRI has been used to localize cerebral generators associated with sensory leg discomfort and PLM in patients with RLS.25 Images were obtained when sensory symptoms were present without movement, when unpleasant sensations were present with movement, and when there were no sensory symptoms or movement. In this study, no structural abnormalities were noted. Sensory discomfort without movement (PLM) was mainly associated with increased activity in the cerebellum and thalamus, with no increased cortical activity. During combined PLM and sensory leg discomfort, patients showed increased activity in these areas and in the red nucleus and brainstem close to the reticular formation.25

Overall, these studies suggest that RLS involves dysfunction in subcortical brain areas, which leads to reduced spinal and possibly cortical inhibition. The changes in spinal excitability may be state-dependent (i.e., they occur more frequently at rest).11

The dopamine A11 cells provide another significant brain area of interest for RLS. These cells extend axons that transverse the entire spinal column26,27 and appear to be involved in several functions, including nociception.28 Lesions in this area have produced some changes in activity that could be seen as paralleling the RLS phenotype,29 but this remains to be more fully evaluated. Certainly the A11 system remains a likely candidate for involvement with RLS. However, when it comes to determining the lesion for RLS, we may have to take the view that the pathology underlying RLS likely involves many brain areas and possibly different neurotransmitter systems other than the dopamine systems that have been evaluated so far.

What Is the Role of Dopamine in the Pathology of RLS?

Given their involvement in sensory and motor regulation, the subcortical dopamine systems, in particular, have been suggested as the areas of primary dysfunction in RLS. The early finding that low doses of levodopa provided complete relief from RLS symptoms focused attention on the dopamine system and strongly supported the hypothesis that...
RLS involves dopaminergic dysfunction in the CNS at the subcortical levels of the brain. Imaging studies have been used to evaluate this hypothesis.

Positron emission tomography studies have shown small but significant reductions of mean caudate and putamen D2-receptor binding and decreased mean putamen 18F-dopa uptake in patients with RLS compared with healthy controls. The finding of only small uptake decreases may reflect the timing of the studies, which were performed when minimal symptoms were present. Balanced against these positive findings are 3 adequately controlled single-photon emission computed tomography studies of striatal D2-receptor binding, 2 of which showed no difference between patients with RLS and controls, while 1 showed a small but statistically significant difference. None of these studies showed any difference for striatal dopamine transporter binding.

Neuroendocrine responses have also assessed dopaminergic function. Prolactin and growth hormone response to a levodopa challenge have been used to investigate dopaminergic function in various disorders. Normally, dopaminergic drugs inhibit the release of prolactin but enhance growth hormone release. Garcia-Borreguero and colleagues used response to these hormones to investigate circadian changes in dopaminergic function in patients with RLS. In their study, following only nighttime administration of levodopa, RLS patients manifested a more pronounced inhibition of prolactin release and an increase in growth hormone secretion compared with normal controls. Unfortunately, the prolactin difference was not statistically significant for the area under the curve, or for any individual point evaluated, once appropriate statistical corrections were made for the number of tests. The growth hormone results are confounded by differences in sleep. However, levodopa-induced inhibition of prolactin plasma levels was significantly correlated with the PLM index on polysomnography. This latter finding supports the possibility of some RLS pathology in the tuberoinfundibular dopamine system that may be related to circadian regulation of that system.

The meager evidence supporting the hypothesized dopamine pathology in RLS seems puzzling given the medication response. It may indicate that we have not identified the major characteristic of the dopamine dysfunction, and, thus, we are not conducting the appropriate tests, or that, in fact, despite the profound symptoms reported, the degree of dopaminergic dysfunction is rather small and difficult to detect.

What Is the Role of Iron in the Pathology of RLS?

For iron to get into the brain, it must be actively transported both across the gut, if given orally, and then across the blood-brain barrier. Transferrin is the primary iron transporter; transferrin receptors are found in high concentrations in the endothelial cells that make up the blood-brain barrier. Ferritin serves both as a storage protein for intracellular iron and as an iron transporter.

Abnormalities of brain iron storage and transport are strongly associated with RLS. In fact, inadequate iron is a common denominator of the 3 major secondary causes of RLS (pregnancy, ESRD, and iron-deficiency anemia). When these conditions resolve, both the iron status and the RLS improve. Recognizing this relation initially led to 2 hypotheses: (1) RLS results from a brain iron insufficiency or iron metabolic abnormality, and (2) all conditions that compromise iron status increase the risk for RLS. The second hypothesis has been generally well documented clinically; the first has now been demonstrated by independently verified studies of both iron-related protein in the CSF and by imaging related to iron content in the substantia nigra. These results have been further supported by a positive clinical response to intravenous iron treatment.

Serum ferritin levels, CSF ferritin and transferrin levels, and MRI measures of regional brain iron have been used to assess iron status in patients with RLS. Ferritin is generally considered to provide a measure of iron storage, with low values indicating low iron storage. Transferrin (the primary iron transport protein in the brain) reflects tissue requirements for iron, with increased transferrin indicating increased demand for iron usually because of decreased iron sufficiency. Thus, brain iron deficiency leads to reduced ferritin and increased transferrin in the CSF. Earley and associates found significantly reduced CSF ferritin and increased transferrin concentrations in patients with idiopathic RLS compared with age-matched healthy controls. Serum iron values, which are highly variable and affected by diet, stress, sleep behavior, and circadian patterns, were within normal limits for both groups. Thus, despite normal serum iron status, all patients with RLS had low CSF ferritin and/or high transferrin levels. This is consistent with the decreased availability of iron in the brain of patients with RLS. These results have been independently confirmed by a Japanese study that reached the same conclusion.

Iron content also varies by brain region. In general, it is greater in dopaminergic brain regions, such as the substantia nigra and striatum. This finding seems reasonable because iron is required as a cofactor with tyrosine hydroxylase in the production of dopamine. In 1 small study, MRI in patients with RLS showed decreased iron stores in the substantia nigra compared with controls. In addition, the decreases in iron were most evident in patients with severe RLS. This finding has been confirmed in a larger sample of patients with early-onset RLS and also in an independent study from Austria using a different method of transcranial ultrasound.

Little is known about the mechanisms controlling iron regulation in the brain. The brain clearly regulates iron on a regional basis, with some areas accumulating large stores of iron with normal aging while others do not. There is also a weak but significant relation between serum and CSF ferritin that is markedly reduced in patients with RLS com-
pared with controls. Thus projections based on this relation in patients with RLS indicate that the serum ferritin value associated with normal CSF values would be >400 μg/L.35,36

MRI findings suggest that local rather than general changes in iron status may account for clinical aspects of RLS. According to Earley and associates,21 regional differences in the distribution of iron in the brain might be owing to lower local thresholds or “set points” for brain iron in patients with RLS. Retention of brain iron within a specific region may mark the difference between patients with and without RLS symptoms. This set-point theory might also explain normal serum iron content in patients with RLS. Although systemic concentrations of iron may be normal in many patients with RLS, these concentrations may not be adequate to maintain brain iron needs because of a lower set point in these individuals. If brain iron is too low, then circadian fluctuations in plasma iron leading to circadian changes in dopamine synthesis may precipitate symptoms of RLS. The investigators concluded that although the causes of alterations in iron regulation are unknown, developmental, environmental, and genetic factors may determine the set point at which levels of iron are established and maintained in various regions of the brain of patients with RLS.21

In addition, iron status has been associated with disease severity. Two studies showed that RLS severity is inversely correlated with serum ferritin levels.23 O’Keeffe and coworkers examined the relation between iron status and RLS in 18 elderly patients with RLS and 18 matched controls without RLS. Serum ferritin levels were significantly lower in the patients with RLS (median, 33 μg/L vs 59 μg/L; P < 0.01). The severity of RLS (based on scores on a self-rating scale of the frequency, degree of distress, and duration of symptoms) was correlated with lower serum ferritin levels. Furthermore, treatment with iron supplements improved symptoms. The greatest degree of decrease in RLS symptoms was found in patients with initial ferritin levels <45 μg/L who received oral iron supplementation (Table 2).23

Sun and associates30 also found that lower ferritin levels were significantly correlated with RLS severity (P = 0.02) and sleep efficiency (P = 0.01). Severity of RLS was rated on the basis of the usual earliest time after 12 noon that the patient experienced either motor or sensory symptoms. Measures of sleep efficiency included the number of PLMS associated with arousal. Similar to the study by O’Keeffe and coworkers,23 the most severe RLS symptoms occurred in patients with low serum ferritin levels (<50 μg/L). In addition, sleep efficiency decreased as serum ferritin decreased.39

What Is the Relation Among Iron Insufficiency, Dopamine Abnormalities, and RLS?

Several areas of research support the connection of decreased brain iron, abnormal dopaminergic function, and RLS. Studies showing decreased iron in certain regions of the brain parallel dopamine imaging studies showing decreased dopaminergic function. Moreover, these abnormalities coincide with the circadian patterns of symptoms in RLS. Decreased availability of iron for dopaminergic cells in the substantia nigra may disrupt cell function and reduce dopaminergic activity at the synapses in the striatum. Therefore, iron insufficiency could be causing dopaminergic dysfunction.11

Animal and human studies on iron support the theory that decreased iron leads to dopaminergic dysfunction. In an important study, 40 male and 40 female rats were fed either an iron-deficient diet or a control diet for 6 weeks. Rats on the iron-deficient diet had decreased densities of dopamine D2- and D1-receptors in the caudate-putamen. The loss of iron in the striatum due to dietary insufficiency was significantly correlated with the decrease in D2- but not D1-receptor density. These studies also demonstrated decreased dopamine transporter function.40 In this rat model of RLS pathology, iron deprivation increased extracellular dopamine and exaggerated the normal circadian changes in amounts of extracellular dopamine. Thus, it is reasonable to hypothesize that RLS may result from brain iron insufficiency with a hyperdopaminergic state.11 Other studies have shown a decrease in Thy1, a protein important for maintaining receptor stability at the cell surface.41 Thus, the dopaminergic problem may involve synaptic dysfunction impairing the signaling process by which striatal dopaminergic cells seek to regulate intrasynaptic dopamine.

The circadian pattern of dopamine and iron metabolism and RLS symptoms further links these factors. Changes in basal ganglia dopamine metabolism associated with iron deficiency are dependent on the time of day.21 Clinically, dopamine and iron levels vary in a circadian pattern.19 Serum iron declines by up to 50% at night. The nighttime decline in serum iron may translate to a clinically important decrease in brain iron levels in patients with RLS, which leads to symptoms.35 Nadirs of both iron and dopamine are reached at the time of maximum RLS symptoms.19

Autopsy studies of the substantia nigra and putamen in patients with RLS compared with controls show results very

<table>
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<tr>
<th>Table 2</th>
<th>Relations of serum ferritin level and change in restless legs syndrome severity scale score in patients treated with iron supplements</th>
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<tr>
<td>Initial Serum Ferritin (μg/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤18</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>6</td>
</tr>
<tr>
<td>Median change in severity score (range)</td>
<td>4 (0–8)</td>
</tr>
<tr>
<td>Change in severity score ≥2 points (%)</td>
<td>5</td>
</tr>
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Adapted from Age Ageing.23
similar to those observed in the iron-deprived rodent model of RLS. These results, both from total nigra samples and from laser capture of only the nigral neurons, show decreased H-ferritin and iron along with increased dopamine and decreased Thy1. Putamen tissue shows decreased D2-receptors with no change in D1-receptors, similar to the profile seen in the iron-deprived animal model.

Finally, iron therapy normalizes changes in dopamine metabolism created by iron deficiency. Correction of peripheral iron levels reduces or resolves the RLS symptoms for many patients.

In summary, the mechanisms by which low brain iron levels cause RLS are not fully established. Clinical and laboratory evidence support a link among dopamine, iron, and RLS. Administration of dopamine antagonists can produce symptoms of akathisia that are indistinguishable from RLS. Dopamine agonists relieve symptoms of RLS. The symptoms have a circadian pattern, predominating at night. Dopaminergic function fluctuates with a diurnal pattern, and serum iron shows a marked circadian variation with a high point at 12 noon and a low point at approximately 8 PM. This time course corresponds to the time course of RLS symptoms.

How Does the Pathology of RLS Relate to Treatment Options?

There are no brain imaging, CSF, or histopathologic studies that have demonstrated primary dopamine deficiency or neurodegeneration in patients with RLS; rather, research suggests a synaptic dysfunction that could lead to either a hyperdopaminergic or a hypodopaminergic state, depending on factors like disease status. Increased extracellular dopamine and, possibly, an increased circadian variation may occur with advanced iron deficiency (as in the animal model) and more severe RLS symptoms. Whether the same dopamine pathology exists for milder iron deficiency, and presumably milder RLS symptoms, remains to be determined. It can be postulated that, during the period of relatively low dopamine levels, postsynaptic adjustment produces decreased activation that could be relieved by dopamine stimulation. In this view, the iron deficiency produces a somewhat unstable system, and this instability has the potential to lead to variable long-term treatment responses.

These considerations support the use of dopaminergic agents for treatment of patients with RLS, while also indicating that RLS augmentation with dopaminergic treatment has to be considered a potentially significant effect of longer-term treatments. Dopaminergic agents are currently the treatment of first choice for patients requiring medication.

Levodopa, a dopamine precursor, is used in conjunction with a dopa carboxylase inhibitor (carbidopa orbenserazide), which increases the availability of levodopa to the brain by reducing its breakdown peripherally. However, levodopa produces profound and disturbing augmentation of the RLS symptoms when given daily at doses of ≥200 mg. Given that risk, newer dopamine agonists are now recognized as alternative first-line therapy. These agents activate presynaptic and postsynaptic dopamine receptors. The ergot-derivative agents that have been used in RLS (bromocriptine, pergolide, cabergoline) act primarily on D2-receptors and have partial or complete D1-agonist properties. The nonergot derivatives ropinirole and pramipexole act mainly on dopamine D2- and D3-receptors. Although these medications have less immediate RLS augmentation than does levodopa, they nonetheless have been shown to frequently produce mild augmentation and, in a very small number of cases, severe augmentation. Aside from this risk, these are generally well tolerated treatments that provide excellent, and sometimes dramatic, relief from RLS symptoms.

For some patients with RLS, the abnormalities in iron metabolism involved in the pathophysiology of RLS respond to dietary or intravenous iron supplementation. Therefore, ruling out iron deficiency is an essential part of any treatment plan for RLS. Administration of iron supplementation may improve RLS symptoms, especially in patients with low ferritin concentrations, and may in some cases produce complete remission of all RLS symptoms.

Summary: What Should Clinicians Know About the Etiology and Pathophysiology of Restless Legs Syndrome?

RLS is fairly common in the US population. The actual prevalence appears to be about 7% to 9% for any frequency of occurrence, and 2.7% to 3% for occurrence with clinically significant symptoms. Two potentially different phenotypes of RLS have been defined on the basis of age at symptom onset. Familiarity with diagnostic criteria and clinical characteristics is essential for diagnosis and appropriate treatment, if required.

The only thing we know with reasonable certainty about RLS pathology is that iron deficiency is somehow involved in at least some cases of RLS. This iron deficiency appears to produce a dopamine dysfunction that may involve disruption of synaptic function, impairing circadian regulation of dopamine. This is reasonable given current data, but it is based on limited studies and must be confirmed in future investigations. The putative dopamine dysfunction is presumably ameliorated by use of dopaminergic medications that often produce dramatic relief from symptoms of RLS. It may also be that the commonly occurring problem of RLS augmentation with dopaminergic treatment reflects a somewhat brittle circadian dysfunction of the dopamine system, but this must be confirmed in future studies. In some cases, especially those associated with iron deficiency, iron supplementation improves or resolves symptoms.
Current Guidelines and Standards of Practice for Restless Legs Syndrome

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ABSTRACT

Algorithms for treatment of restless legs syndrome (RLS) include both nonpharmacologic and pharmacologic therapy. Patients with RLS are divided into 3 groups: (1) those with intermittent RLS symptoms; (2) those with daily RLS symptoms; and (3) those whose symptoms are refractory to standard treatments. Many patients do not require medication, and symptoms often can be relieved with good sleep hygiene and avoidance of medications and factors that provoke symptoms. Recent large-scale clinical trials have proved the efficacy of therapy for RLS when it is required. Several classes of medications are helpful, but dopaminergic therapy appears to be most effective and relieves symptoms rapidly. The first step in managing RLS is to ensure that there is an adequate diagnosis; this involves discriminating RLS from other conditions that may share a number of features. Finally, it is important to tailor treatment to the needs of each individual patient. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Anticonvulsants; Dopaminergics; Opioids; Restless legs; Sedative-hypnotics; Treatment

Treatment of restless legs syndrome (RLS) is a rapidly developing field. Only since the beginning of the 21st century have large-scale multicenter trials in RLS become common. In May 2005, ropinirole became the first drug approved by the United States Food and Drug Administration (FDA) for treatment of RLS.

The first evidence-based standards for RLS treatment were promulgated by the American Academy of Sleep Medicine (AASM) in 1999.1 These guidelines recognized that RLS was a serious sleep disorder and that practitioners—at least sleep specialists—should become familiar with RLS, be able to diagnose the condition, and understand how to provide appropriate management. Moreover, these guidelines acknowledged that treatment for RLS would be chronic and might require occasional adjustment of treatment. However, these 1999 standards, which were based on a review of therapeutic trials through 1998,2 did not recognize that any treatment had risen to the level of general acceptance and strong recommendation. The more recent 2004 standards3 are limited to dopaminergic treatment, because almost all trials between 1998 and 2002 (the cutoff date for the evidence-based review4) had studied the use of a dopaminergic drug. However, the 2 most highly recommended agents in that review, levodopa and pergolide, have since been recognized as having more limited value. At the time, ropinirole, the first agent in the United States indicated for RLS, still had the low-level endorsement of an “option,” and was not yet recommended for treatment. In November 2006, pramipexole became the second dopamine agonist approved for treatment of RLS by the FDA.

In 2004, the Medical Advisory Board of the RLS Foundation promulgated an algorithm for treatment of RLS5 that was based on both completed trials (including some unpublished trials) and expert opinion. Because of the ability to incorporate clinical experience and trials not yet published, this algorithm was closer to current expert practice. The basic scheme was to divide patients into 3 groups: (1) those with intermittent RLS symptoms; (2) those with daily RLS symptoms; and (3) those whose symptoms were refractory to standard treatments. The suggested algorithm incorporated both nonpharmacologic and pharmacologic management. The general
Avoiding Medications that Provoke RLS

A number of medication classes have been known to aggravate RLS. Dopamine-blocking agents, including neuroleptics, are known to provoke RLS symptoms, but antiemetics, antinausea medications, gastrointestinal medications (such as metoclopramide), and some sedatives can also aggravate RLS. This may be of particular importance during surgical procedures or diagnostic tests, when a dopamine blocker may be used for sedation. Physicians should make patients aware of this possibility and discuss it ahead of any procedure to avoid difficulties during the procedure.

Antihistamines, such as diphenhydramine, can also aggravate RLS. Drugs in this class may be found in a variety of over-the-counter preparations, including sleep aids, allergy medications, and medications for nasal congestion or upper respiratory tract infections. Patients should be alerted to read ingredient labels carefully before using these medications.

Table 1 Nonpharmacologic management of restless legs syndrome (RLS)

- Find any underlying disorders and treat, if feasible
- Eliminate precipitants of RLS
  - Dopamine-blocking agents (neuroleptics, antinausea compounds, metoclopramide)
  - Antidepressants (selective serotonin receptor inhibitors, tricyclics)
  - Antihistamines
  - Common stimulants and depressants: caffeine, alcohol, nicotine
- Practice good sleep hygiene
  - Regular sleep and wake times
  - Restrict bed to sleep and intimacy
  - Avoid perturbing activities immediately before sleep
- Use simple behavioral interventions
  - Brief walk before bedtime
  - Hot bath or cold shower
  - Massage of limbs
- Moderate exercise: neither inactivity nor unusual and excessive exercise, which may precipitate RLS
- Weight management: healthy diet and adequate activity
- Information and support: Web sites and patient support groups

Adapted from Mayo Clin Proc. 5

scheme of this review will closely follow the recommendations of the RLS Foundation’s algorithm.

NONPHARMACOLOGIC APPROACHES

Treatment of RLS begins with an assessment of potential factors in the patient’s life that may aggravate RLS. These issues must be detected and either eliminated or modified. Table 1 summarizes nonpharmacologic approaches to addressing these factors. 5

Behavioral Strategies

Various survival practices and attitudes may assist patients living with RLS. Helpful guidance has been well developed by a patient with RLS who maintains a Web site (www.rlsrebel.com). An entire program of behavioral suggestions has now been published in a book by this patient-expert. 6

Support and Information

The RLS Foundation maintains a network of patient support groups that can be found in most major cities in the United States and Canada. The Foundation’s Web site (www.rls.org) is a major source of information for physicians and patients. The RLS Foundation publishes a medical bulletin and a scientific bulletin for physicians as well as a patient bulletin. The Foundation also has booklets on RLS in general and on issues of special concern, such as the effects of RLS on children, surgery, and depression.

Sleep Hygiene

Sleep hygiene involves a number of practices that enhance the ability to sleep. The major recommendation is the development of a routine, such that sleep is attempted at the same time each day after a period of reduced activity. A hot bath or other brief activity before bed may also be helpful. It is especially important that patients with RLS avoid sleep deprivation, because this may increase symptoms. The goal of sleep hygiene, then, is to allow the patient with RLS to get an optimal amount of sleep.

Lifestyle Modifications

Evidence for the usefulness of lifestyle modifications is derived only from anecdotal reports and clinical impression. It appears that caffeine and nicotine can aggravate RLS. Alcohol, especially if consumed in the evening, often can worsen RLS symptoms. Patients should be alerted to the possible effects of these common stimulants and sedatives, because avoiding or reducing their intake may improve RLS symptoms. Individuals should also be encouraged to incorporate a moderate level of exercise into their daily routine. Many patients experience an increase of symptoms later in the evening, after extensive exercise during the day, but some epidemiologic studies have suggested that lack of any exercise is positively associated with exacerbation of RLS symptoms. In general, a healthy lifestyle—including moderate exercise and dietary practices as recommended to diminish risks of cardiovascular and metabolic disease—is likely a good choice for patients with RLS.
PHARMACOLOGIC THERAPIES

Although nonpharmacologic strategies may work for patients with milder symptoms, or for exceptional patients who are able to overcome their symptoms, most individuals with moderate-to-severe symptoms will require some medication to make symptoms tolerable. The first goal of RLS management is to provide for adequate restorative sleep that occurs at desirable and appropriate times. Through achievement of this goal, many daytime symptoms, such as fatigue, lack of concentration, sleepiness, and even depression, may be resolved. A secondary goal is to enable patients with RLS to enjoy the kinds of quiet, relaxing, and passive activities that most readily evoke symptoms (e.g., reading, watching TV, attending the theater, traveling by car or plane, having a dinner party).

Matching Drugs to Symptom Severity

As indicated by the RLS Foundation’s algorithm (Table 2), intermittent symptoms (e.g., occasional bouts that last for days or under certain provocative situations such as long-duration travel) can be managed by medications taken on an as-needed basis. If symptoms are situational, or if they can be predicted from a prodrome (sense of impending symptoms) or clear pattern (e.g., after vigorous physical activity or at a phase of the menstrual cycle), medications can be taken in anticipation of their occurrence. The recommended medications include levodopa (with a decarboxylase inhibitor), mild- to moderate-strength opioids, or sedative-hypnotics (if symptoms occur during the sleep period). Dopamine agonists may work for some individuals, but they usually have a longer onset of action, making them less useful if taken after symptoms develop. Levodopa has a shorter duration of action and may wear off during the night, resulting in recurrence of symptoms, a phenomenon known as rebound.

Frequent, and especially daily, symptoms may require patients to take medications on a daily basis. Currently, dopamine agonists are the first-line treatment for daily RLS symptoms. A viable alternative is gabapentin, the first clinically tested drug among a number of possibly satisfactory anticonvulsants. Patients can also be managed with mild- to moderate-strength opioids. Some patients with more moderate symptoms can be managed with sedative-hypnotics. Levodopa is usually not useful for daily RLS because many patients develop an iatrogenic worsening of RLS called augmentation.

Patients who fail initial attempts at daily treatment, especially those who cannot tolerate dopamine agonists because of side effects or augmentation, may require a change of medication. This may mean use of a different agonist, a moderate-strength opioid, or gabapentin. Combination therapy, often with reduction of the agonist dose, also may be useful. A sedative-hypnotic is commonly added to the agonist, but a large variety of combinations of drugs from different classes have also been tried. In the most severe cases, strong opioids, such as methadone, have proved useful.

The Main Drug Classes: Benefits and Drawbacks

Recommended doses for the various drugs used in RLS are given in Table 3. Although the most extensive clinical experience has been with use of dopaminergics, it is important to consider the full range of treatments shown to have efficacy in RLS.

Dopaminergics

The first dopaminergic used in RLS was levodopa (along with a decarboxylase inhibitor). Levodopa remains an excellent medication for occasional use or low-dose treatment (maximum 200 mg/day) of patients with very mild symptoms or for patients who have only periodic limb movements in sleep, but the frequent development of augmentation renders it less useful for daily treatment. However, the dopaminergic side effects of nausea, lightheadedness, headache, or sleepiness are less of a problem with levodopa than with the dopamine agonists.
Compared with levodopa, dopamine agonists generally have longer half-lives. Sustained-release or patch preparations of agonist agents, with coverage up to 24 hours, are currently being developed. Thus, these drugs are especially useful for patients whose symptoms present for a more sustained period. The earliest agonists, bromocriptine and pergolide, are ergoline derivatives and have recently been implicated in heart valve disorder and fibrotic syndromes. Cabergoline, also an ergoline-derivative and pergolide, are ergoline derivatives and have more sustained period. The earliest agonists, bromocriptine, which has shown good activity in all aspects of treatment, has the advantage of highly sustained action (40-hour half-life) and may cause less augmentation during treatment. However, even with the ergoline derivatives, it is prudent to monitor cardiac function during treatment.

As a result of their potential adverse effects on cardiac function, ergoline drugs have recently ceded place to the nonergoline agonists. Two nonergoline derivatives, ropinirole, are currently approved for use in either Europe or the United States. Their side effects are generally milder than those of pergolide, but they generally require some titration to reach the effective dose. It appears that achievement of effective dose titration may be more rapid with pramipexole.

Several other dopaminergics have been tested in patients with RLS. Apomorphine can be given as a subcutaneous preparation and has a rapid onset of action. Two patch preparations, rotigotine and lisuride, are currently under development. These drugs offer the advantage of continuous release, which may also reduce augmentation. Perhaps because patients with RLS have a normal dopamine system and use much lower doses compared with patients who have Parkinson disease, the typical severe parkinsonian side effects of dyskinesias, hallucinations, sleep attacks, and psychosis appear to be only very rare problems in RLS. Hypersexuality and uncontrolled gambling, sometimes seen in Parkinson disease, have also not been important limitations.

### Opioids

Compared with dopaminergic drugs, the evidence for opioids is meager. However, most experts find that opioids can be useful, without much risk for addiction, although patients must be monitored for development of dependence. Patients given long-term treatment with opioids should also be monitored for development of respiratory problems. Other potential side effects include sedation, urinary retention, or constipation. The benefits of methadone treatment in patients with the most severe symptoms have been highlighted in a recent report. Intrathecal morphine has also been used in some patients. Tramadol, which is active on both the opioid and serotonin systems, has been used quite commonly, perhaps because it is not as tightly regulated as other medications.

### Anticonvulsants

Tegretol was the first anticonvulsant to be studied, which led to its recognition in a therapeutic guideline in the first AASM standards report. Currently, however, it is not often prescribed for RLS. A newer option in this class is gabapentin, which has shown good activity in all aspects of RLS and has demonstrated equivalent efficacy to ropinirole in one study. Gabapentin is generally well tolerated, but it can cause sedation in all patients as well as ataxia in older individuals. Other anticonvulsants may be worth considering, but there is relatively little evidence to date to support their use, although trials of some of these agents are ongoing.

### Sedative-Hypnotics

Clonazepam was among the first medications to be tested for treatment of RLS, but it has not been the subject of more recent trials. There is even less evidence for other sedative-hypnotics. However, some patients find these drugs helpful, and they may be quite useful if given in combination with other agents.

### Iron

Because iron deficiency and reduced brain iron levels are common in RLS, oral iron supplementation is an established treatment. Ferrous sulfate (325 mg) given with vitamin C (250 to 500 mg) 3 times daily between meals is the recommended regimen, if tolerated. Gastrointestinal discomfort, especially constipation, is the major drawback, and many RLS patients appear refractory to supplementation. Recently, use of intravenously administered iron has been investigated, but this remains a somewhat experimental treatment. It is indicated, however, if the patient has true iron deficiency, which can occur even with normal-range ferritin levels.
Other Agents
Other classes of medications are being explored for RLS, but to date the only reported evidence is for clonidine.38 The investigators in this randomized, double-blind, placebo-controlled study found that clonidine is mostly useful for symptoms at bedtime.

SPECIAL PATIENT POPULATIONS
A number of patient groups warrant special attention because of concerns that may complicate the management of their RLS symptoms.

Pregnant Patients
Because pregnancy evokes RLS, especially in the third trimester, it represents a therapeutic concern. Pregnant patients may have folate and iron deficiency, which can be remedied. No medication is completely safe in pregnancy, but some of the opioids can be used with relative safety. Use of these drugs may be restricted to the most severe cases and delayed until the third trimester but warrants consideration, because the sleep disruption of RLS may itself cause complications of prematurity and difficult delivery.39

Children
Few children have RLS that requires pharmacologic treatment, but studies in children have been quite rare. It is best to begin with good sleep hygiene and caffeine restriction (including restriction of caffeinated soft drinks). Dopaminergic drugs have been shown to improve RLS symptoms in children.40 In cases of associated attention deficit/hyperactivity disorder (ADHD), the dopaminergics may benefit ADHD symptoms as well.40

Patients with Secondary RLS
The most common causes of secondary RLS are iron deficiency or anemia, uremia, and pregnancy. Although patients with secondary RLS may require treatment for their RLS symptoms, resolution of the causative condition often resolves the RLS. In most cases of pregnancy, for example, new-onset RLS will resolve soon after delivery.41 Dialysis does not improve RLS in uremia, but transplantation does.42

WHAT SHOULD INTERNISTS KNOW ABOUT MANAGEMENT OF RESTLESS LEGS SYNDROME?
For the primary care physician treating patients with RLS, understanding a few critical points is key to effective management.

Treatment Depends on Diagnosis
The first step in managing RLS is to ensure the adequacy of diagnosis.9,10,43 This involves discriminating RLS from other conditions that may share a number of the same features.

Tailor Treatment to the Patient
Treatment depends on whether RLS is primary or secondary and on whether it is caused by iron deficiency. In the latter case, iron replacement should be considered. As mentioned previously, many patients do not require dopaminergic medications; in these individuals, nonpharmacologic approaches may be sufficient and successful. For patients who require dopaminergic therapy, the choice of treatment should take into account the frequency and timing of symptoms. It is always best to anticipate symptoms and to give drugs at a suitable time before symptoms are likely to begin. Most agonists have a longer time to onset, compared with levodopa and most sedative-hypnotics, and must be given ≥1 hour before expected onset of symptoms.

Use Low Doses of Dopaminergics
The dose range for use of dopaminergics in RLS (Table 3)9,10 is well below that typically used in patients with Parkinson disease. In fact, the maximum doses that would ordinarily be considered for RLS are the minimum effective doses in Parkinson disease. In treating patients with RLS, it is best to “go low and slow,” increasing doses of medications every few days to once a week. This strategy may help avoid missing a therapeutic window and also may reduce potential side effects or complications. It has been suggested that some of the drugs have a U-shaped response curve, meaning that higher doses will not work as well as lower ones.44

Patients with Severe Symptoms and the Problem of Augmentation
If continuous increases in the dopaminergic dose become necessary, or if the problem of augmentation appears, it is important not to simply increase the dose but to use a strategy appropriate for refractory patients. Augmentation is the most important complication of dopaminergic treatment. It is essential that the physician recognize augmentation when it occurs, because it can result in significant adverse effects for the patient.

When to Refer
Each individual physician must decide when he or she reaches the limits of comfortable management. I strongly believe that most internists and family physicians can diagnose RLS, provide primary therapy for both intermittent and daily symptoms, and use a variety of medications tailored to different symptom patterns. However, each physician must decide whether to get involved with more refractory patients who may require complicated adjustments of medication. When treatment of the patient poses greater than ordinary difficulties, such as unmanageable augmentation or the need for stronger opioids, it is appropriate to refer the case to a recognized RLS expert.

SUMMARY
Treatment for RLS is rapidly evolving. Only as recently as May 2005 did the first FDA-approved treatment become available. A better understanding of the pathophysiology of RLS will facilitate the development of new therapeutic
agents. It is essential that clinicians remain informed and continually update their knowledge about RLS so that they can render the best possible care for their patients.

References

A Better Future for Patients with Restless Legs Syndrome

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ABSTRACT

Despite advances in the management of restless legs syndrome (RLS), there still is a great deal of uncertainty about its etiology, pathophysiology, therapy, and clinical outcomes. Much remains to be learned. Future research on these issues will help identify the optimum therapeutic approach for the diverse group of patients with RLS. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Dopaminergic agonists; Gabapentin; Pramipexole; Restless legs syndrome; Ropinirole

Despite remarkable advances in the recognition and treatment of restless legs syndrome (RLS) over the past 20 years, there is still a great deal of uncertainty regarding its pathophysiology, etiology, epidemiology, and clinical outcomes. Specific research, including studies yielding better information on the pathophysiology of RLS, is necessary to further define the condition and approaches to treatment. Proposed criteria for diagnosis in special populations must be validated. Large-scale, longitudinal studies in different populations of patients with RLS are required to further our understanding of its natural history. Greater knowledge about the factors that modify the condition (e.g., family history, age at onset, presence of neuropathy) is also needed. In addition, more information is required regarding the use of treatments other than dopamine agonists and the management of patients who are pregnant or undergoing dialysis. The role of iron supplementation, especially for those who do not have serum iron deficiency, is another area for future research. The development of tolerance and augmentation associated with use of dopaminergic and nondopaminergic treatments are the major complications of therapy for RLS. Therefore, to help physicians prescribe dopamine therapy most appropriately, it will be important to design prospective placebo-controlled studies with validated scales for augmentation and tolerance. Future studies in RLS also should prospectively compare dosing with long half-life or continuous-release agents against nocturnal dosing, so as to assess the evolution of symptoms under these 2 treatment conditions. In addition, there is a need to prospectively evaluate the effects of drug withdrawal and reinstitution, as well as to evaluate strategies for rotating drugs into the regimens of patients experiencing side effects, tolerance, or augmentation issues. Finally, other areas of research, including brain and genetic studies, should be considered.

New standards of care and clinical guidelines continue to be established by different professional groups for the management of patients with RLS. For example, the International Restless Legs Syndrome Study Group (IRLSSG) (http://irlssg.org/) and the Movement Disorder Society (MDS) (http://www.movementdisorders.org/) are professional organizations committed to advancing knowledge in this field.
about the causes, pathogenesis, and clinical impact of RLS. Such organizations have been responsible, at least in part, for the growth of information about RLS and the increase in familiarity with the disorder. Finally, it is important to educate patients about resources that can help them and their families cope with RLS. One such resource is the RLS Foundation (www.RLS.org). Other organizations include We Move (www.wemove.org/rls) and the National Sleep Foundation (NSF) (www.sleepfoundation.org).

Farther down the RLS pipeline are several rich clinical therapeutic developments. Transdermal patch continuous-release and oral controlled-release forms of dopaminergic agents will soon be in final registration trials. Similarly, trials of dopaminergic agonists with more specific receptor profiles, as well as those with both noradrenergic and dopaminergic effects, may begin in the near future. Large FDA registration trials of anticonvulsant medications, which are often used off-label for RLS and for chronic pain, are currently in progress. In the future, synthetic opioids with dopaminergic agonism may also be tested in RLS.

Finally, given the success of intravenous iron therapy in an open-label trial in idiopathic RLS\(^4\) and in a double-blind placebo-controlled trial in renal failure–related RLS,\(^5\) we should soon be hearing about larger, more rigorous, controlled studies of this approach.

References
Supplement to
The American Journal of Medicine

Recognizing and Treating Restless Legs Syndrome: Current Standards

CME SECTION

ASSESSMENT TEST
AND EVALUATION FORM

Sponsored by:
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CME ASSESSMENT TEST

Recognizing and Treating Restless Legs Syndrome: Current Standards

Please circle the correct response to each question on the Answer Sheet provided. A passing score of ≥70% must be achieved to receive CME/CE credit. There is no fee for participation in this educational activity.

1. What percentage of patients with restless legs syndrome (RLS) symptoms are appropriately diagnosed?
   a. 5%
   b. 25%
   c. 50%
   d. 75%

2. Which of the following describes 2 major features of RLS?
   a. Urge to move and circadian variation of symptoms
   b. Urge to move and inability to sleep
   c. Pain in the legs and inability to sleep
   d. Circadian pattern of symptoms and pain in the legs

3. Which of the following statements is correct?
   a. Individuals with a family history of RLS generally have a later onset of RLS symptoms.
   b. In individuals with late-onset symptoms, RLS progresses more rapidly with advancing age.
   c. Early-onset RLS symptoms occur before 20 years of age.
   d. Patients with earlier-onset RLS generally have much more severe symptoms compared with patients who have late-onset RLS.

4. Which best describes the essential criteria for diagnosing RLS?
   a. Urge to move legs usually accompanied or caused by uncomfortable or unpleasant sensations in the legs
   b. Urge to move or unpleasant sensation partially or totally relieved by movement as long as activity continues
   c. Urge to move or unpleasant sensation worse in the evening or night than during the day or only occur during the evening or night.
   d. All of the above

5. Which of the following medications can provoke symptoms of RLS?
   a. Neuroleptics
   b. Metoclopramide
   c. Antidepressants, especially selective serotonin reuptake inhibitors
   d. Antihistamines
   e. All of the above

6. Which of the following statements is true?
   a. Patients with intermittent symptoms can be managed by medications taken on an as-needed basis.
   b. Levodopa is preferred to, and has a longer duration of action compared with, dopamine agonists.
   c. Currently, gabapentin is the first choice treatment for frequent or daily symptoms.
   d. Patients who fail at initial attempts at daily treatment require a potent opioid.

7. Which is the recommended approach for treatment of RLS in pregnant women?
   a. Folate and iron deficiency should be remedied
   b. Some opioids can be used with relative safety
   c. All pregnant women should receive treatment for symptoms because sleep disruption from RLS may itself cause difficulties with prematurity and delivery
   d. All of the above
   e. a and b

8. According to the RLS Epidemiology, Symptoms, and Treatment (REST) studies, what is the prevalence of RLS symptoms?
   a. Approximately 6% to 12%
   b. Approximately 5% to 10%
   c. Approximately 2.5% to 11%
   d. Approximately 10% to 14%

9. What is the role of iron in the pathology of RLS?
   a. Abnormalities of brain iron storage and transport are strongly associated with RLS.
   b. Iron status has been associated with disease severity.
   c. RLS severity is inversely correlated with serum ferritin levels.
   d. All of the above
   e. a and c

10. Which of the following statements is correct?
    a. Dopaminergic function fluctuates with a diurnal pattern.
    b. Serum iron shows a marked circadian variation with a high point at 12 noon and low point at approximately 8 PM.
    c. RLS symptoms have a circadian pattern, predominating at night, which correlates with dopaminergic function fluctuations and serum iron levels.
    d. All of the above
    e. a and b
CME ASSESSMENT TEST ANSWER SHEET

Recognizing and Treating Restless Legs Syndrome: Current Standards

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2. Were the educational objectives met?
   —Discuss the etiology of primary and secondary restless legs syndrome (RLS) □ Yes □ No
   —List key clinical features in the clinical presentation of RLS □ Yes □ No
   —Diagnose RLS according to current standard criteria □ Yes □ No
   —Develop an RLS management plan according to symptom severity and impact on the patient’s life □ Yes □ No
   —List currently available first-line and alternative treatments for RLS □ Yes □ No

3. Is this activity free of commercial bias? □ Yes □ No

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