References

Dear Colleague,

Restless legs syndrome (RLS) garnered considerable interest at this year’s annual meeting of the Associated Professional Sleep Societies (APSS) Meeting which was held June 5 through June 10 in Philadelphia. Throughout the oral presentations, discussions, symposia, and poster sessions a common thread emerged: RLS is a prevalent and burdensome disorder that is highly treatable. Spurred on by the dynamic advocacy of the Restless Legs Syndrome Foundation, scientific investigation has now reached sufficient maturity so that data from several large, controlled trials are available to support evidence-based decisions. These trials, some of which were presented at this meeting, demonstrate that medications have emerged to manage RLS motor symptoms and sleep difficulties, as well as improve quality of life. Diagnostic guidelines for RLS for adults and children, based on the four core URGE criteria, have played a significant role in standardizing diagnosis and helping clinicians to distinguish RLS from other “mimic” disorders. The new treatment algorithms developed by the Medical Advisory Board of the RLS Foundation, introduced at APSS, should become invaluable guides for clinicians treating patients with RLS.

The groundswell of attention over the last decade that has led to better recognition of RLS and development of agents that target the underlying pathophysiology of RLS is good news for the approximately 31 million American adults and children who are afflicted by this disorder. In this newsletter we highlight the latest news and views about RLS, direct from APSS.

Sincerely,

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Target Audience
This activity is designed for clinicians who treat patients with sleep disorders.

Activity Goal
The goal of Expert Perspectives in RLS: News and Views from the 2004 Associated Professional Sleep Societies (APSS) Annual Meeting is to provide clinicians with the key clinical data and insights on the diagnosis and treatment of RLS from the APSS Annual Meeting.

Series Objectives (based on content from all 5 parts of the series)
• Incorporate the latest data on RLS epidemiology, and genetics and other risk factors, into identification and diagnosis of patients at risk for the disease.
• Differentiate between RLS and other disorders such as peripheral neuropathy based on clinical presentation and the results of polysomnography.
• Identify RLS in special populations, including children, pregnant women, and patients with other conditions such as ADHD.
• Formulate diagnosis and treatment strategies for patients with co-morbid disease.
• Develop an effective RLS treatment plan based on safety and efficacy data of available therapies.
• Translate an understanding of the latest data on RLS pathophysiology into selection of appropriate treatment strategies

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Introduction

Restless legs syndrome (RLS) is a troublesome neurologic disorder that is frequently underrecognized and poorly treated. Patients with RLS complain of disturbing motor symptoms and sleep difficulties, which profoundly affect their daily function. Research presented at APSS highlighted new data about the epidemiology and management of RLS, including the presentation of new treatment algorithms. Considerable focus was given to RLS in special populations, including children and those with depression or end-stage renal disease.

Epidemiology

The variability in prevalence figures for RLS appears to at least partly reflect whether the patients come from a general, primary care, or sleep-disorders clinic population. Published general population studies have reported RLS prevalence of about 10%.[1] At APSS, Lainey and colleagues reported that 8.5% of 10,263 French adults in a population-based survey met International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria.[2] Studies of RLS in primary care populations have reported somewhat higher prevalence of 11% to 24%,[3] which may be due to increased reporting of symptoms by patients, said Clete A. Kushida, MD, PhD, of Stanford University.

Although RLS is a prevalent disorder, it remains underreported and undiagnosed. Richard P. Allen, PhD, of Johns Hopkins University in Baltimore, Maryland, for example, reported at APSS that even in patients who had symptoms two or more times a week that were at least moderately distressing, only 64% had consulted a physician about their symptoms and only 8.1% had been diagnosed with RLS.

RLS prevalence also appears to differ by geographic region or ethnicity. Compared with RLS prevalence in Western European or US populations, data presented at APSS reported that RLS is less common in Asian populations. Oka and colleagues[4] reported that the prevalence of RLS among the elderly in Japan was 1.4%, similar to published findings of 0.6% in the general population and 0.1% in a primary care population in Singapore,[5] <1% in Japan,[6] and 3.2% in Turkey.[7]

Risk Factors

Advancing age is associated with increasing RLS prevalence and severity. One study reported RLS prevalence in 3% of adults aged 20 to 29, with peaks of 14% at age 50 to 59 and 19% after age 80.[8] Female gender also appears to increase the risk of developing RLS, especially with increasing age and increasing parity.[9]

There also appears to be a genetic predisposition to developing RLS. RLS is often familial and most studies show an autosomal dominant form of inheritance, which may be associated with chromosomal abnormalities at 12q and 14q. At APSS, David B. Rye, MD, PhD, of Emory University School of Medicine described his work on the genetic linkage of RLS in Iceland. Because of several factors, including its fairly homogeneous population, extensive record-keeping system, and willingness of people to participate in clinical studies, the population of Iceland is well suited for this analysis. Dr. Rye’s preliminary results[10] suggest that RLS in people living in Iceland may be more severe than generally seen elsewhere, as indicated by high occurrence of symptoms in the arms, frequent onset before age 30, and a high incidence of affected first-degree relatives.

In his presentation, Dr. Kushida reviewed evidence that RLS is also associated with, and sometimes caused by, medical conditions (Table 1). At one APSS poster session, Gyorfi and colleagues from Budapest, Hungary, reported on RLS in 19 patients with rheumatoid arthritis (RA).[11] Thirty percent of the patients...
manifested symptoms of RLS. Although no correlation was found between inflammatory activity of RA and clinical severity of RLS, low serum ferritin values (<50 µmol/L) correlated well with RLS symptom severity, supporting the theory that iron deficiency may play a role in RLS. Gillis et al from Henry Ford Hospital in Detroit showed that 25% of a group of 737 patients on hemodialysis met IRLSSG diagnostic criteria. Only 8.1% of the sample had been diagnosed with RLS and 2% were being treated for it.¹⁵

Medications, including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), lithium, antihistamines, and atypical and typical neuroleptics, can also precipitate RLS. In her presentation at the Postgraduate Course on Current Standards for Diagnosis and Treatment of RLS, Dr. Phillips identified lifestyle risk factors that are associated with RLS, including drinking more than three alcoholic beverages per day, smoking more than 20 cigarettes per day, obesity, and exercising fewer than 3 hours per month.

**Diagnosis of RLS in Adults**

Philip M. Becker, MD, comments:

*Very few patients come to a sleep medicine clinic saying they have restless legs syndrome. More commonly, patients will complain that they cannot sleep or they snore. The challenge for any physician is to ask the right questions. Since RLS is one of the primary medical reasons for poor sleep, the clinician must ask about the four URGE criteria. Patients may not report they have restless legs because they either do not believe they have a problem that requires a doctor's attention or they think they have a problem that cannot be fixed. Some patients may think that their sleep problem is due to depression or anxiety, and they are reluctant to identify themselves with those problems.*

The diagnosis of RLS can be made clinically, by ascertaining the presence of all four obligatory diagnostic features of RLS, as formulated by the International Restless Legs Syndrome Study Group (IRLSSG).¹⁶ These features can be summarized by the URGE acronym (Table 2). A sleep study is not necessary to make the diagnosis, but may be needed to rule out other causes.

According to Barbara A. Phillips, MD, MSPH, from the University of Kentucky in Lexington, most RLS patients report sensations in their legs that have been described as creepy, crawly, tingly, painful, burning, achy, “like worms or bugs crawling deep in the muscle,” or “like water running under the skin,” which are associated with a compelling urge to move. Symptoms usually affect both legs simultaneously but can be unilateral or alternating. The arms are sometimes involved. RLS symptoms usually have a characteristic circadian pattern, with peak symptom severity between midnight and 4 AM and marked relief between 6 AM and 10 AM.

Three additional clinical features support, but are not necessary for, RLS diagnosis. These include positive response to dopaminergic therapy, a family history of RLS, and the presence of periodic limb movements of sleep (PLMS). In her presentation, Dr. Phillips explained that most patients with RLS will show a strong response, at least initially, to a trial of levodopa or dopamine agonist, such as pramipexole or ropinirole. In his presentation, Dr. Allen took the issue one step further, suggesting that if a patient does not respond to a trial of a dopaminergic, the diagnosis of RLS must be questioned. Since RLS patients have a three to five times greater chance of having a first-degree relative with RLS, compared with those who do not have RLS symptoms,¹⁷ a positive family history is important diagnostically, especially for patients who develop RLS before age 45.

Two subjective scales are commonly used to measure RLS. One is a 10-point scale created by the IRLSSG, known as the IRLSSG Rating Scale (IRLS), that has been validated by comparison with independent clinician ratings in a large multicenter study. Scores can range up to 40, with 5 to 15 considered mild, 15 to 25 considered moderate, and >25 indicative of severe RLS. The other, the Johns Hopkins Restless Legs Severity Scale, is a one-question test that focuses on the time of day symptoms appear. At APSS, Allen noted that the advantages of the Hopkins scale are that it allows retrospective evaluation easily and allows identification of augmentation.

Clete A. Kushida, MD, PhD, comments: *RLS can be easily diagnosed in a primary care physician’s office by using the four IRLSSG criteria. A sleep study is not necessary for diagnosis and is not indicated for RLS unless the person also has suspicion of periodic limb movements during sleep and daytime impairment, such as fatigue, inability to concentrate, or difficulty in focusing.*

### Table 1. Conditions Associated with RLS (% with RLS)

- Iron deficiency anemia (25%)
- End-stage renal disease (20%–57%)
- Polyneuropathy/radiculopathy (37%)
- Rheumatoid arthritis (25%–30%)
- Diabetes (24%)
- Parkinson’s disease (20%)
- Pregnancy (11%–33%)
- Polyneuropathy/radiculopathy (37%)
- Pregnancy (11%–33%)
- Diabetes (24%)
- Rheumatoid arthritis (25%–30%)
- Parkinson’s disease (20%)
- Pregnancy (11%–33%)

### Table 2. RLS: Core Symptoms “URGE”

- Urge to move limbs, usually accompanied or caused by uncomfortable and unpleasant feelings in the limbs
- Rest or inactivity precipitates or worsens symptoms
- Getting up or moving improves the sensation
- Evening or nighttime appearance or worsening of symptoms
Periodic Limb Movements of Sleep (PLMS)

Barbara A. Phillips, MD, MSPH, comments: The relationship between PLMS and RLS has intrigued researchers and clinicians for some time. The vast majority of patients with RLS have PLMS, if they go to the sleep lab and are assessed for it. However, PLMS are a fairly nonspecific finding—they are common in normal people without sleep complaints and are virtually ubiquitous in people over age 80. It’s important not to confuse PLMS with RLS, and PLMS do not establish a diagnosis of RLS. Another important take-home message is that the number of PLMS does not correlate with RLS severity.

PLMS are repetitive, stereotypic, involuntary movements, primarily of the legs, that occur during sleep. According to data reported by Wayne Hening, MD, PhD, of the Robert Wood Johnson Medical School in New Jersey, PLMS occur in a series of at least 4 movements, each movement generating an EMG potential lasting 0.5 to 5 seconds, with a 5- to 120-second interval between movements. The minimum amplitude of the EMG potential is 25% of the maximum voluntary contraction of the Anterior Tibialis muscle.

Studies indicate that approximately 80% of RLS patients will have more than 5 PLMS per hour, with the greatest frequency occurring during the first few hours of the night. However, in her presentation, Dr. Phillips emphasized that PLMS are common and nonspecific, and are neither necessary nor sufficient to make a diagnosis of RLS. PLMS should not be considered a motor marker for RLS. For instance, Phillips cited a number of studies reporting on PLMS prevalence in other sleep disorders. These include data by Jacques Montplaisir et al. that PLMS > 5 can be detected in 80% of patients with narcolepsy, 40% of insomniacs, 30% of hypsomniacs, and 55% of healthy controls, and data by Ancoli-Israeli et al. that the prevalence of PLMS increase with age so that 45% of those over age 65 demonstrate PLMS > 5. At APSS, Skomro and co-workers at the University of Saskatchewan in Canada showed that 16.7% of 79 patients with congestive heart failure manifested PLMS > 5.

Does quantifying PLMS play a role in diagnosing RLS?

Objective tests to measure PLMS remain ancillary in diagnosing RLS. Such tests, eg, polysomnography (PSG) or actigraphy with PSG, can measure the amplitude and frequency of PLMS. In his presentation, Allen suggested that a good activity meter should be able to mark each leg movement, not just give total counts, and should be sensitive enough to separate small leg movements from walking. At APSS, a poster by Gschliesser and colleagues from University Hospital in Innsbruck, Austria, found that the Actiwatch actometer significantly underestimated PLMS in comparison to the gold standard, PSG.

Several APSS participants discussed the Suggested Immobilization Test (SIT) as a measure of both subjective discomfort and leg kicks repeatedly during a period of wakefulness (usually 1 hour). During one session, Wayne Hening, MD, PhD, observed that, during a SIT test, RLS patients, unlike controls, showed a progressive increase in sensory discomfort and involuntary periodic movements, known as periodic limb movements of wakefulness (PLMW). Jacques Montplaisir, MD, PhD, CRCpc, of the Hopital du Sacre-Coeur de Montreal in Canada, reported that controls typically have SIT scores up to 15 while RLS patients may have scores of 50. Dr. Montplaisir, who is currently evaluating SIT sensitivity in a large trial, commented that he expects standardized instructions for the SIT to soon be available on the web.

Several speakers indicated that PLMs of wakefulness may be more diagnostic of RLS than PLMs of sleep. A suggested criterion for RLS diagnosis is PLMW > 40. Montplaisir reported that combining both PLMWs and SIT discomfort measures allows a diagnosis of RLS that is 82% sensitive, 100% specific, and correct 88% of the time. In a poster, Montplaisir, et al. also provided evidence that PLMWs have an inverse relationship to age, which suggests that detection of PLMWs is a good supportive measure for RLS in older patients.

Do PLMS have clinical significance and, if so, should they be treated?

PLMS are frequently associated with arousals, as described by Dr. Allen at APSS. He noted that increases in heart rate and blood pressure and EEG activation can be detected even before the start of a PLM. However, it is unclear whether these episodic arousals cause sleep disruption, hypersomnolence, or other adverse, clinically meaningful, consequences. Dr. Montplaisir indicated that as a general rule he does not treat PLMS, but does treat associated sleep problems.

Under what circumstances should a patient suspected or diagnosed with RLS be referred to a sleep disorders center?

Since RLS is a prevalent condition, primary care physicians will often be able to manage it. Dr. Allen explained that referral for a sleep evaluation is appropriate when co-existing sleep disorders, such as sleep apnea, REM behavior disorder, or narcolepsy, is suspected. A sleep evaluation can also provide helpful information when a diagnosis of RLS is uncertain or when the patient does not respond to standard treatment.

Barbara A. Phillips, MD, MSPH, comments: The clinician sometimes wonders what to do with PLMS that are encountered on a sleep study, when RLS is not in the differential diagnosis. I do not treat asymptomatic PLMS. I certainly will treat PLMS if the patient has symptoms of RLS, I would not treat PLMS associated with other sleep disorders, such as narcolepsy, sleep disorders breathing, or REM behavior disorder, with a dopaminergic agent. Another, more subtle question, and one that clinicians do wrestle with, is do we treat PLMS in a patient who is sleepy or fatigued but does not have symptoms of RLS? The jury is still out, but my personal view is that we should not treat PLMS if the main symptom is...
sleepiness, because data have consistently shown that the number of PLMS, even if they are associated with arousals, does not correlate with sleepiness.

Distinguishing RLS from Clinical Mimics

Sometimes people with medical conditions other than RLS appear to satisfy the four core RLS criteria, commented Wayne A. Hening, MD, PhD, during a presentation at APSS. These mimic conditions may include leg cramps, akathisia, positional discomfort, and local leg pathology. To distinguish RLS from other conditions, clinicians should first be cognizant of the typical RLS presentation, and during the history ask patients about arthritis, sciatica, leg injury, impaired circulation, or varicose veins. Question the patient about the type of sensation, methods the patient uses to obtain relief, time and frequency of symptoms, and whether the discomfort is related to position or cramping. Legs should be examined for tenderness, scars, varicose veins, pulses, swollen joints, lost reflexes, weakness, and areas of sensory loss.

Leg cramps are sometimes confused as RLS. Both tend to occur at night, in bed, and are relieved by movement, explained Hening. However, leg cramps are usually brief, intermittent, and severe with a localized spasm, while RLS tends to last longer with no actual spasms. Complaints of restlessness can sometimes be attributed to nervousness or anxiety, which is usually not localized to the legs, or neuroleptic-induced akathisia.

During the Postgraduate Course “RLS Associated with Other Disorders or In Special Populations: Treatment and Diagnostic Considerations,” William G. Ondo, MD, from the Baylor College of Medicine in Houston, Texas, highlighted the differences between neuroleptic-induced akathisia, which requires a history of neuroleptic use, and RLS. Unlike RLS, akathisia affects the entire body, is associated with the use of dopamine antagonists and with parkinsonism. There is also no significant nighttime exacerbation of symptoms and there is no family history of a similar disorder.

Positional pain, due to either compression/tension or ischemia (leg going to sleep), usually occurs with a fixed position, such as sitting, and may be aggravated by local injury, explained Hening. Changing position usually relieves positional pain, and these patients are not compelled to walk, stretch the legs, or bend the legs as in RLS. Discomfort due to local leg pathology such as arthritis, fractures, torn ligaments, or peripheral neuropathy is generally not relieved with activity, can be temporally associated with a specific cause, and is not accompanied by the urge to move.

Philip M. Becker, MD, comments: Neuropathy and RLS are often difficult to distinguish. About one third of RLS patients have peripheral neuropathy, and neuropathy is easily missed in many of these patients. Some ways to separate the two disorders is to determine if the condition can be relieved by leg movement (yes for RLS, no for neuropathy) and if symptoms are present in the early morning hours (no for RLS, yes for neuropathy). Patients with RLS and neuropathy are likely to benefit from gabapentin. To differentiate RLS from akathisia, look at the distribution of symptoms: the whole body is affected by akathisia while RLS symptoms affect mainly the legs and arms.

Quality of Life with RLS

A satellite symposium on RLS, entitled “The Thief of Sleep,” featured Pickett M. Guthrie, a founder of the RLS Foundation, who eloquently described the isolation and ridicule she experienced living with RLS. Before diagnosis and treatment, she was limited by poor sleep, hours of nocturnal restlessness, intense discomfort, fatigue, depression, and sleepiness. She could not travel on an airplane and she avoided the theater or concerts. Pickett noted a strong family history of RLS, attributing the death of her father in a motor vehicle accident to sleepiness resulting from his own uncontrolled RLS. When her daughter began developing symptoms in her twenties, Guthrie felt compelled to take action and, in conjunction with some fellow RLS sufferers, organized the RLS Foundation. The RLS Foundation (www.rls.org) now has more than 75,000 individuals in their database and works with affected individuals, the public, and healthcare professionals to publicize, educate, and support research in RLS.

Dr. Allen elaborated on quality of life considerations in RLS. He cited data from the REST study which surveyed more than 23,000 primary care patients. Of those, slightly less than 10% reported weekly RLS symptoms. Almost 90% of those with RLS reported sleep problems, 82% uncomfortable feelings in the legs, 57% inability to sit still, and 54% pain. Sleep problems included latency to fall asleep, frequent awakenings, and decreased sleep time. During the day, those with RLS reported they lacked energy, could not sit still, were depressed, and could not carry out some activities of daily living.

In his own research, Allen surveyed 200 RLS patients attending a sleep disorders center, to look at sleep and cognitive functioning. Using the SF-36, a generic instrument used to measure quality of life, Allen found that patients with RLS were impaired in all subscales. Furthermore, the degree of impairment was comparable to that seen for other serious chronic medical conditions, including congestive heart failure, angina, hypertension, chronic obstructive pulmonary disease, and diabetes. Compared with US published norms, patients with RLS had sleep-related problems as well as cognitive problems, such as reasoning, forgetfulness, concentration, and confusion. As RLS severity increases, more problems are seen with both sleep and cognition. Allen concluded that while sleep and cognitive problems were correlated, cognition appears to be directly impacted by RLS and not only indirectly from sleep disturbance.

Clete A. Kushida, MD, PhD, comments: We know that RLS does have a significant impact on quality of life for patients, in terms of affecting their ability to concentrate and their
vitality throughout the day. Two recent studies presented at APSS that focused on quality of life issues in RLS have shown that areas such as sleep disturbance, sleep quality, sleep improvement, and daytime somnolence are improved in RLS patients with treatment by the dopaminergic agonist ropinirole.

Pathophysiology of RLS
Dopaminergic Systems
Numerous pharmacologic studies have demonstrated that dopaminergic agonists reduce RLS symptoms while dopaminergic antagonists exacerbate RLS symptoms. While pharmacologic studies form the basis of support for the theory that RLS involves a disruption of subcortical dopamine systems, other approaches have had inconsistent results. In one presentation, Dr. Allen commented that two of four imaging studies demonstrated decreased D2 receptor binding, but two studies measuring dopamine metabolite levels in the cerebrospinal fluid (CSF) of RLS patients provided no results in support of the dopamine theory.

Iron deficiency
Iron deficiency is known to be a secondary cause of RLS and, therefore, considerable interest at APSS focused on the role of iron in the pathophysiology of RLS and the therapeutic possibilities of iron supplementation. According to Dr. Allen, many of the major secondary causes of RLS, including anemia, end-stage renal disease, pregnancy, and gastric surgery, have one thing in common: iron deficiency. Furthermore, he postulated that any condition that compromises iron sufficiency increases the risk of RLS.

Iron deficiency is marked by increased levels of transferrin and transferrin receptors, and decreased levels of ferritin. Serum measures of ferritin and CSF measures of ferritin and transferrin are clinically useful for assessing iron status in patients. Research studies have also utilized magnetic resonance imaging (MRI) measures of regional brain iron and postmortem neuropathology. Many reports support the thesis that RLS patients appear to have iron deficiency. Studies have shown that RLS severity and serum ferritin levels are inversely correlated, and treating patients with oral iron improves RLS symptoms. Allen's work has demonstrated that CSF ferritin levels are decreased and transferrin levels are increased in RLS patients compared to normals. Nichols and co-investigators at Stanford University compared ferritin levels of 59 age and gender-matched primary care patients with or without symptoms of RLS. They found that mean ferritin levels for RLS positive patients were significantly lower than those of RLS negative patients (P < .03).

Phil. M. Becker, MD, comments: In my practice, about 15% to 20% of my patients have clearly abnormal ferritin levels of <17 mcg/L. I recommend that any patient with moderate to severe restless legs is deserving of iron studies, such as ferritin levels and TIBC. Patients undergoing iron supplementation should have liver function studies as well, because that is where iron is stored. Ferritin levels should be checked every 3 months to avoid the problem of hemochromatosis, which may affect one out of ten patients of northern European descent.

Clinical Indicators of Iron Deficiency
Dr. Allen recommended that all restless legs patients should undergo two lab measurements: serum ferritin and percent iron saturation during the initial work-up and, if the patient is iron deficient, routinely retested during treatment. Ferritin levels can give a good indication of iron status and percent iron saturation can be used to monitor for hemochromatosis.Iron deficiency may be indicated by ferritin <18 mcg/L, % saturation <16%, or Total Iron Binding Capacity (TIBC) >400. Clinicians should note that ferritin levels can be acutely elevated during inflammation, and query patients about possible infections at the time of testing to avoid false positives. While hemoglobin levels may identify anemia, it is a poor indicator of iron deficiency. Serum iron, which varies with diet and time of day, is also a poor indicator. Changes in transferrin levels and TIBC are not considered useful because they only show change as iron deficiency becomes severe. Measuring transferrin receptor levels is probably the best way to determine iron status, but the tests are too expensive for routine use.

Current Treatment Issues in RLS
Barbara A. Phillips, MD, MSPH, comments: I think a lot of what is driving the interest in RLS that I see at this meeting is the development of newer, more effective, more specific agents. I saw at least four different new agents in studies reported in the poster session today, and also saw some alternative agents. There were data about herbals and about external counter-pulsation for the treatment of RLS. Clinicians are reluctant to look for a condition for which they have no effective treatment. I think the awareness that we now have treatment that works rapidly, effectively, and safely will help us to identify patients that can get this treatment and benefit from it. The most exciting agents now, of course, are the new dopaminergic agents, and hopefully we'll have a drug with an FDA indication within the next year to treat RLS.

In the past, RLS research was criticized because of a paucity of data from large, controlled trials hindered the formulation of evidence-based treatment strategies. That situation appears to be changing, with presentations of the
results of several large trials described at APSS, which provide new and/or better data to support the use of RLS treatments.

Philip M. Becker, MD, presented the results of a retrospective chart review that looked at treatment of RLS patients. This review of all patients seen between 2000 and 2002 identified 64 patients with RLS who had been treated for at least 15 months. Almost three quarters were judged by clinicians to have symptoms that were moderate to very severe. With treatment, 82% were "much" or "very much" improved, with more than 60% becoming virtually symptom free. By methodically targeting symptoms, Becker reported that most RLS patients achieved stable therapy within 3 to 6 months. In his practice, 30% of RLS patients were managed with single agents, most commonly the nonergot dopamine agonists pramipexole and ropinirole or an opiate. The majority of patients required combination therapy, usually a dopamine agonist plus a sedative-hypnotic.

In a review of single medication treatments, Arthur S. Walters, MD, of the New Jersey Neuroscience Institute at JFK Medical Center, said that the decision to treat RLS is based upon patient request. Treatment may be necessary to alleviate motor symptoms, reduce sleep disturbances, or complaints about reduced quality of life, with the ultimate goals of allowing patients to sit still for longer periods, engage in social and leisure time activities, sleep better, and improve cognitive function. The decision to treat PLMS should be based on signs of accompanying EEG arousal and awakening on PSG, and on symptoms of interrupted nocturnal sleep or daytime fatigue. PLMS > 5 per hour of sleep with associated arousals is a generally accepted indication for treatment.

Iron Treatment of RLS

The first step before initiating treatment is to determine the cause of the deficiency, and then work to correct the problem. Iron supplementation may begin even before the underlying problem is corrected. When RLS is due to iron deficiency associated with pregnancy, the woman may wish to forgo treatment once she understands that in most cases the RLS will resolve after giving birth.

The benefit of oral iron appears to depend on initial ferritin levels, explained Christopher Earley, MD, PhD, of Johns Hopkins School of Medicine. If ferritin is <50 mcg/L, oral iron will probably help but for those patients with ferritin levels of 60 mcg/L or more, oral iron may not change iron levels significantly and may cause constipation and other adverse side effects. Current guidelines for oral iron supplementation are oral iron sulfate 350 mg plus Vitamin C 200 mg taken two or three times daily on an empty stomach. Treatment should be stopped when ferritin levels reach >50 mcg/L or % saturation >50%. Allen cautioned that because there may be a long delay of 6 to 8 weeks before seeing a response, RLS patients on oral iron therapy may also require dopamine medication to control symptoms during this time.

Some RLS patients may benefit from intravenous iron therapy. Earley and Allen presented data from an open-label trial showing that repeated IV dosing of iron 1000 mg (Ferrlecit®) on an as-needed basis reestablished RLS symptom control in 3 patients whose symptoms had returned, and helped to normalize the excessive rate of ferritin decline that had been seen following the first IV treatments. Earley emphasized that this treatment was still experimental and not ready for clinical practice in treating RLS. However, treatment of the iron deficiency is an approved indication.

Dopaminergic Medications

Background

In general, dopamine agonists and levodopa are now the first-line treatments for both idiopathic and familial RLS, except for those with very mild intermittent symptoms. This practice dates from 1982 when Akpinar serendipitously found that RLS symptoms responded to levodopa. Since then, according to Claudia Tienkwalder, MD, of the University of Goettingen in Germany, who spoke at “The Thief of Sleep” symposium, there have been at least 11 controlled treatment studies (Level I-III) with 195 patients and 9 open treatment studies (Level V) showing that levodopa combined with either carbidopa or benserazide provides dramatic and rapid control of RLS symptoms, PLMS, or both. Due to the risk of augmentation developing from chronic use as well as its short duration of action, levodopa is only given occasionally as needed for intermittent RLS symptoms or conditions producing symptoms breaking through the usual satisfactory treatment. Walters says that depending on patient tolerance, carbidopa/levodopa may be increased from an initial dose of 10/100 mg or 25/100 mg or 25/250 mg 1 tablet at the hour of sleep to a regimen of 1 tablet 2 hours prior to the hour of sleep, 1 at the hour of sleep, and 1 in the middle of the night as needed.

The dopamine agonists have generally proven to be effective agents for the treatment of RLS, with longer durations of action and less risk of augmentation or rebound than levodopa. These agents include two ergot-derived agents, bromocriptine and pergolide, and two nonergot medications, pramipexole and ropinirole.

Clete A. Kushida, MD, PhD, comments: For the treatment of patients with moderate to severe cases of restless legs syndrome, the most common and most effective treatment of restless legs syndrome in 2004 is to use a dopaminergic agonist such as ropinirole or pramipexole. The reason why this class of medication has supplanted use of levodopa is because levodopa has been shown to have a greater rate of augmentation and rebound. Second-line treatment for restless legs syndrome includes benzodiazepines, opiates, or anti-convulsants. But the most effective and most common mode of treatment in 2004 is the use of dopaminergic agents.
News from APSS on Dopaminergic Agents

**Pergolide**

Claudia Trenkwalder, MD, from Georg August University in Goettingen, Germany, presented the results of a recently published, double-blind, placebo-controlled randomized trial of 100 patients with RLS looking at the effect of pergolide on RLS and PLMS. In the first phase that measured change from baseline to week 6, pergolide (0.25 to 0.75) significantly improved RLS symptoms, sleep efficiency, and quality of sleep, and decreased PLMS and PLMS associated with arousal. Effects on PLMS were maintained for 12 months for 29 of 33 patients who responded initially to pergolide. Pergolide was generally well tolerated; nausea and headache were reported more frequently than placebo.

**Pramipexole**

Partinen and colleagues from the Rinnekoti Research Centre in Espoo, Finland presented the results of dose-finding study of pramipexole, looking at both RLS symptoms and PLMS. The study was a 3-week double-blind placebo-controlled study in which patients received once daily either placebo or pramipexole, at 0.125 mg, 0.25 mg, 0.5 mg, or 0.75 mg. A total of 109 patients were randomized to receive either placebo or pramipexole at each of the 4 doses. Significant decreases in the Periodic Limb Movement Index (PLMI) and Restless Leg Syndrome Rating Scale (RLSRS) were noted for all dose groups compared with placebo (Figs. 1a and 1b). Clinical efficacy based on RLSRS score and responder rate (≥50% reduction in RLSRS) was most prominent in the 0.5 mg and 0.75 mg groups. Pramipexole was generally well tolerated, with some increase in the rate of nausea seen compared with placebo.

**Ropinirole**

Montplaisir and colleagues looked at the long-term efficacy of ropinirole in a 36-week study of 282 patients with primary RLS. Patients received 24 weeks’ of single-blind ropinirole treatment, during which ropinirole was titrated to its optimal therapeutic dose (range: 0.25 to 4.0 mg/day). At the end of the single-blind phase, 92 patients were randomized to a double-blind phase of ropinirole vs placebo. This study looked at symptom severity, quality of life, and sleep measures. These researchers observed that the odds of a patient relapsing while receiving placebo were three times greater than those of a patient receiving ropinirole. Patients treated with ropinirole were more likely to be “much” or “very much” improved on the Clinical Global Impression-Improvement (CGI-I) scale than placebo-treated patients. Quality of life showed improvement with ropinirole on both the generic SF-36 and disease-specific RLSQoL scales. Sleep parameters, which were measured with the Medical Outcomes Study (MOS) sleep scale, showed less sleep disturbance and daytime somnolence, and better sleep quantity and sleep adequacy during the single-blind phase; these benefits deteriorated in patients who were switched to placebo after receiving ropinirole. Most adverse events were mild or moderate in severity, with nausea and headache the most common adverse events. Three patients experienced augmentation with ropinirole, which resolved spontaneously as treatment continued.
Ropinirole has a rapid onset of action, as documented by a poster presentation by Philip M. Becker, MD. Using data from three large double-blind clinical trials (n = 618), Becker was able to show significant improvements on the CGI-I and IRLS within 1 week of treatment, compared with placebo. These effects were seen even at low doses (0.25–0.5 mg/day).

Montplaisir’s group was not the only one looking at the effect of ropinirole on sleep. Richard P. Allen, MD, utilized the data from the same three large double-blind clinical trials as Becker. Like the Montplaisir study, Allen found that RLS patients treated with ropinirole reported subjective improvements in sleep quality and quantity, as measured by the 4 MOS sleep scale domains (adequacy, quantity, disturbance, somnolence) after 12 weeks of treatment.

Trenkwalder presented data from the recently published TREAT RLS 1 study. This was a 12-week, randomized, placebo-controlled study of 284 patients with RLS ≥ 15 on the IRLS, which was carried out in 10 European countries. At APSS, Trenkwalder showed that although RLS reduces sleep duration and sleep adequacy, as measured by the MOS, ropinirole treatment (mean dose 1.90 ± 1.13 mg/d) restores these variables toward US population norms (Figs. 2a and 2b).

The effect of ropinirole on leg movements was documented in a PSG study by Richard P. Allen and colleagues, a study in press in Sleep. Twenty-nine patients with RLS were treated with ropinirole and 30 received placebo for 12 weeks. Ropinirole significantly (P < .01) decreased PLMS and PLMS of arousal compared with placebo; the number of RLMS reached normal levels for age with ropinirole. Significant decreases in PLMs of wakefulness were also noted with ropinirole.

Clete A. Kushida, MD, PhD, comments: It has been estimated that about 40% report that the sleep disturbance is the primary morbidity of restless legs syndrome; that, in fact, the effect of RLS on sleep is the most troublesome symptom of RLS. A recent study by Allen showed that ropinirole, a dopaminergic agonist, can reduce the sleep disturbance by almost twice as much compared with placebo, improves sleep quality by providing an extra 42 minutes of sleep each night, improves sleep adequacy by about three times compared with placebo, and reduces the daytime sleepiness by about twice compared with placebo. So, ropinirole can provide some benefit to one of the most troublesome symptoms of restless legs syndrome, which is the disturbance of sleep.

Cabergoline

Cabergoline is a novel ergot alkaloid that is not available in the United States. In a small open study, carbergoline reduced PLMS of arousal and sleep efficiency. Trenkwalder presented the results of a 5-week placebo-controlled unpublished study involving 84 patients with RLS, looking at the effect of cabergoline (0.5 mg, 1.0 mg, and 2.0 mg) on the IRLS. Significant decreases with all doses were noted after 1 week of treatment and which lasted through the 5-week trial.

Agents Under Investigation

Lisuride, a dopamine agonist used for parkinsonian patients, is available as a transdermal patch, which is supposed to provide continuous and reliable...
dopaminergic stimulation. Benes from Neurological Hospital in Schwerin, Germany looked at the effect of lisuride patches on patients with severe RLS. In a small (n = 10), short-term study consisting of a 2-week open label phase and a 1-week double-blind phase, lisuride was efficacious as assessed with the IRLS and RLS-6 severity scales, the CGI, the Epworth Sleepiness Scale, and a sleep questionnaire, as well as PLMS measured by actimetry.

Apopomorphine is a combined opioidergic and dopaminergic agonist. In an exploratory study, apomorphine (bolus of 0.035 mg/kg body weight followed by a constant infusion rate of up to 0.04 mg/kg/h) significantly improved subjective RLS symptoms during the SIT and reduced EMG-documented PLMWs during a 1-night PSG study (n = 9). The authors say more work is needed to understand whether the effect of apomorphine is mediated by the dopamine or opioid systems, or both.

Augmentation and Dopaminergic Agents

In Dr. Becker’s discussion of features and treatment strategies for augmentation, he reviewed the criteria for augmentation (Table 3). Augmentation may occur in up to 80% of RLS patients treated with levodopa, while about 30% to 35% develop augmentation with dopamine agonists. Because daily dosing with levodopa can lead to severe augmentation in the majority of RLS patients, caution and careful monitoring are required if levodopa is used daily. A new Augmentation Severity Rating Scale (ASRS) developed by the European Affiliate of the IRLSSG under the guidance of Diego Garcia-Borreguero, MD, Luigi Ferini-Strambi, MD, and Claudia Trenkwalder, MD, was distributed at the “Thief of Sleep” symposium.

Management strategies for augmentation include lowering the dose of the dopaminergic, if possible. Serum ferritin levels should be checked for possible iron deficiency, and treated if present. In mild to moderate augmentation, an earlier dosing of the dopaminergic may help, at least temporarily. Another option would be the use of a dopaminergic with a longer half life. Discontinuing the dopaminergic agent and switching to gabapentin or an opiate may be necessary to alleviate augmentation, especially in severe cases.

Anticonvulsants for RLS

Background

Gabapentin is the most effective of the anticonvulsants in the treatment of RLS, and gabapentin is the anticonvulsant of choice for RLS, stated Dr. Walters. It is effective both as a single agent and in combination with dopamine agonists or opiates. Gabapentin is considered a treatment of first choice where pain is a major component of RLS symptoms. Use of gabapentin is limited by its high cost, tendency to produce sedation, and necessity for TID dosing due to its short duration of action. Double-blind studies have shown that carbamazepine (200 to 600 mg/d) alleviates leg sensations of RLS and improves sleep latency and sleep efficiency, but has little beneficial effect on PLMS, says Walters. Carbamazepine has many serious side effects such as neutropenia and liver dysfunction that also restrict its use. Other anticonvulsants, such as lamotrigine (100 mg/d) and valproate (125 mg to 600 mg/d) suppress PLMS or associated sleep fragmentation.

Philip M. Becker, MD, comments: I would have to agree that double-blind, placebo control trials [have shown gabapentin to be effective for RLS]. My problem is, in my clinical practice, I’ve not seen the same potential benefit. There are some potential explanations why gabapentin has not been as good. Gabapentin is extremely variable in its absorption. The other issue that is important is that the dosages often have to be quite high, and patients may have side effects that prevent it from being something they could tolerate during certain times of their day.

New at APSS

Oxcarbazepine has a similar chemical structure to carbamazepine, but does not cause neutropenia or liver dysfunction. Youssef and Walters treated 17 RLS patients with oxcarbazepine (600 mg/d to 1500 mg/d, average 900 mg/d) as an open label monotherapy or add-on drug for RLS. Four patients dropped out of the study. For the remaining 13 patients, IRLS scores dropped from 28.9 at baseline to 9.1 after treatment. The authors plan to continue this work by conducting a blinded study of oxcarbazepine.

The effect of the anticonvulsant levetiracetam on RLS was evaluated by Lacey in a small open-label trial. Levetiracetam was given as a single dose 3 hours before bedtime according to the following schedule: 500 mg for 2 weeks, 1000 mg for 2 weeks, and then 1500 mg for 2 weeks. Of the 7 of 10 patients who completed the trial,
IRLSSG scores fell from 26.07 at baseline to 18.42 at the end of the 500 mg arm, 16.14 at the end of the 1000 mg arm, and 13.71 at the end of the 1500 mg arm. Improvements were also seen on the Epworth Sleepiness Scale and the CGIC. Further controlled studies are planned.

**Opioid Therapy for RLS**

**Background**

There is some evidence, mostly pharmacologic, to support the hypothesis that there is a hypofunction of the endogenous opioid system in RLS. As a general rule, opioids improve RLS symptoms, and administration of the rapidly acting opioid receptor blocker naloxone to opioid-treated patients exacerbates RLS symptoms. Opiate medications are often used as treatments of second choice for RLS, or for those who have developed augmentation on dopaminergic treatment. They may also be used as a first treatment if there is a major component of pain associated with the RLS. There have been no large clinical trials of opiates for RLS.

**New at APSS**

Dr. Becker presented his views of which opioids are best for the treatment of RLS. In order of decreasing efficacy, Becker found levorphanol > hydromorphone > hydrocodone > propoxyphene. (Fig. 3) Walters indicated that in his practice he frequently uses codeine or oxycodone, and may use methadone for patients with very severe RLS. He cautions that these drugs can exacerbate sleep apnea. Oxycodone and methadone are rated Category B and may be used cautiously in pregnant women with RLS. There were no research studies providing new data on the use of opioids for RLS presented at APSS this year.

**Sedative-Hypnotics for RLS**

Sedative-hypnotics are considered second-line therapy for RLS, with use limited to those with mild symptoms or young patients. The therapeutic benefit from sedative-hypnotics for patients with RLS appears to be promoting sleep sufficiently to override RLS-induced arousals, not from effects on restless legs movements. Because of their soporific properties, benzodiazepines must be used with caution in the frail or elderly.

At APSS, Walters said that sedative-hypnotics should be considered the least effective class of agents for RLS, compared with dopaminergics, opioids, or anticonvulsants. Of the sedative-hypnotics, he prefers the use of clonazepam (0.5 to 2 mg/d), which has been shown in double-blind studies to suppress PLMS. He suggested 0.5 mg clonazepam initially with gradual increases as needed, up to 4 mg/d in divided doses. Triazolam (0.125 to 0.5 mg) may be even more effective in controlling PLMS of arousal and improving sleep efficiency. Short-acting agents such as zolpidem or zaleplon may be useful to minimize next-day sedation.

**Nonpharmacologic Options**

**Background**

While patients with RLS and PLMS often try a variety of nonpharmacologic treatment strategies, nonpharmacologic treatments have generally failed to consistently provide significant relief. There are virtually no controlled studies looking at nonpharmacologic interventions. One strategy that patients can adopt is improving sleep hygiene, such as maintaining regular and appropriate sleep and wake times, regulating time in bed, controlling light exposure during the night, minimizing late-day caffeine, nicotine, and alcohol, and reducing the length of daytime naps. Other strategies are arranging work schedules so that they are awake during the time of worsening symptoms, exercising in moderation, and performing tasks to increase arousal (eg, knitting, eating popcorn at the movies). Avoiding provocative situations, such as sitting in a car for hours, may help avoid the emergence of symptoms.

**New at APSS**

External Counter Pulsation (ECP), in which 3 sets of leg cuffs placed on the calves and upper and lower thighs are sequentially inflated and deflated, is used in patients with angina refractory to medical therapy and who are not surgical candidates. Noting that ECP sometimes helped RLS in these patients, Rajaram and colleagues at the NJ Neuroscience Institute looked at the effect of ECP in 5 patients with angina or congestive heart failure on RLS symptoms. ECP was given 1 hour per day for 35 days. They found the average IRLS rating scale decreased from 29.2 at baseline to 7.2 after 35 days of ECP (P < .001). Two patients had complete symptom resolution and many of the patients reported improvement that lasted for months. The authors suggested that ECP produced changes in vascular flow which influenced the peripheral or central nervous system leading to changes in RLS symptomatology. Larger double-blind studies are in progress.

![Figure 3. Efficacy of Different Opioids in Treatment of RLS](image-url)
Cuellar looked at the use of herbs, natural products and complementary and alternative practices and products (CAPPS) in persons with RLS. Using a convenience sample of 40 adults recruited from support groups, Cuellar found that 65% of the sample used CAPPS. The most commonly used biologically based CAPPS were Vitamins E, C, B, and multivitamins. Other CAPPS used included prayer, exercise, meditation, and music. The author says that the study suggests a high prevalence of CAPPS use among persons with RLS to decrease symptoms that are unmanageable by conventional pharmacologic agents.

Treatment Algorithms

Philip M. Becker, MD, comments: *I think the treatment algorithms proposed by the medical advisory board of the RLS Foundation will prove quite helpful to physicians so they will understand when they can offer behavioral or pharmacologic options to their patients. One comment I might have is that for daily symptoms, I believe the initial therapy should be a dopamine agonist such as ropinirole or pramipexole.*

At APSS, Dr. Trenkwalder and Dr. Becker both presented algorithms for the treatment of RLS that were developed by the Medical Advisory Board of the Restless Legs Syndrome Foundation. These recommendations are based on expert opinion, but cannot be considered evidence-based because there are not enough trials of sufficient strength yet available. Three algorithms were shown, Algorithm 1 for the treatment of mild, intermittent RLS, Algorithm 2 for daily RLS symptoms, and Algorithm 3 for refractory RLS. (Figs. 4, 5, and 6) The first algorithm for mild intermittent symptoms includes both nonpharmacologic options as well as medications (ie, benzdiazepines, low-potency opioids, levodopa, and dopamine agonists). The algorithm for daily symptoms includes nonpharmacologic therapy as well the low-potency opioids, dopamine agonists, and gabapentin, first as monotherapy and then in combinations.

**Refractory RLS**

If a patient becomes refractory to a specific RLS treatment, Algorithm 3 suggests other pharmacologic options. Clinicians should also consider other reasons for treatment resistance, including psychiatric co-morbidities (eg, depression), other co-morbidities (obstructive sleep apnea, neuropathy, insomnia, other sleep disorders), secondary causes of RLS (eg, iron deficiency), and problems with medication (incorrect dosage, reduced effect due to other medications or foods, poor compliance, adverse effects).
RLS in Special Populations

Depression

Clete A. Kushida, MD, PhD, comments: We know that depression is fairly common in RLS patients. It can affect about a third to half of RLS patients. The real problem with the treatment of depression in RLS is that the medications that are used to treat depression can often worsen RLS in patients that have both of these conditions. In particular, SSRIs and TCAs can increase symptoms of RLS, as well as increase the PLMS that frequently accompany RLS. The study by Yang showed that bupropion can actually reduce the number of PLMS during sleep compared with other antidepressants.

Daniel Picchietti, MD, of the University of Illinois College of Medicine in Champaign-Urbana discussed the relationship of RLS, PLMS, and depression. Referring to 12 published reports which all reported higher rates of depression symptoms in RLS patients than controls, Picchietti says that about 40% of RLS patients complain of symptoms of depression. There is less evidence of whether RLS is more common in patients with depression, although Picchietti cited one study that found 26% of depressed patients had RLS. It is unclear at this time whether RLS is causing depression, if sleep disruption due to RLS is causing depression, if depression is causing RLS, or if both disorders share a common dysfunction of one or more neurotransmitter systems.

An important issue when treating a patient with RLS for depression is that SSRIs, TCAs, and lithium have all been associated with inducing PLMS, even in healthy controls. In contrast, bupropion has been reported to decrease PLMS. Antidepressant-induced PLMS may be responsible for complaints of insomnia in depressed patients taking medication, and may limit treatment compliance. At APSS, Yang and colleagues’ from Brigham and Women’s Hospital in Boston compared the effects of antidepressants on leg movements in patients referred to a sleep clinic for PSG. They found that serotoninergic antidepressants such as citalopram, fluoxetine, sertraline, paroxetine, and venlafaxine induced PLMS, but the noradrenergic/dopaminergic agent bupropion did not. Therefore, if a patient on an SSRI complains of worsening PLMS, the clinician is advised not to raise the dose of the SSRI (which may exacerbate the problem) but to consider switching to bupropion.

Picchietti presented several treatment guidelines for managing depression in patients with RLS. Nonpharmacologic approaches which may improve sleep, such as better sleep hygiene, moderate exercise, and cognitive behavioral therapy, can benefit both RLS and depressed mood. He suggests RLS patients with mild depression should not be treated with an antidepressant or should be weaned from the antidepressant once RLS symptoms are controlled. These patients may benefit from pramipexole, which has been found to improve depression symptoms in RLS patients (mean dose 0.28 mg at night). Picchietti says that pramipexole has been used as a single agent therapy for depression at doses somewhat higher than used for RLS (1 to 5 mg per day). Mildly depressed patients may also benefit from the sleep consolidating effects of sedating antihistamines. Sleep consolidation also helps to prevent depression relapse.

Bupropion should be considered for RLS patients with major depression and who are not on an SSRI. It is an effective antidepressant equivalent to SSRIs, with less risk of somnolence or sexual dysfunction, and should be given in the morning to minimize its stimulant effect. Medications to consolidate sleep may also be used. For patients with major depression already on an SSRI, clinicians should consider switching to bupropion, although some patients may still need low doses of the SSRI for complete symptom control. The SSRI should be tapered slowly to avoid withdrawal. Clinicians may also consider adding an antidepressant with a more adrenergic mechanism of action, such as desipramine.

The Restless Legs Foundation has just published a new brochure entitled “Special Considerations in Treating Depression when the Patient has Restless Legs Syndrome.” Copies of the brochure can be obtained by contacting the Foundation at www.rls.org.

Patients on Hemodialysis in End-Stage Renal Disease (ESRD)

Barbara A. Phillips, MD, MSPH, comments: Some presentations at this meeting have addressed the very high prevalence of RLS in people with renal failure. I’m glad to see that this area is getting some attention, because this is a group that has an extraordinarily high prevalence of RLS symptom and whose quality of life is very much compromised by their underlying disease. RLS symptoms are exacerbated by having to lie still, and dialysis requires people to lie still. We now have a dopaminergic agent, ropinirole, which is hepatically cleared, which could be used for patients with renal failure on hemodialysis without affecting dialysis schedule and without really having to recalculate their dose. That’s an advantage for this population.

RLS can make a difficult situation almost intolerable for people undergoing hemodialysis in end-stage renal disease, who must sit in one place with minimal movement for 3 to 4 hours at a time three times a week. Sadly, the consequences of RLS in these patients may lead a patient to become less compliant with dialysis, and increase the risk of mortality, according to John W. Winkelman, MD, PhD, of the Sleep Disorders Program at Brigham and Women’s Hospital. Winkelman presented data showing that ESRD patients with RLS and/or PLMS showed a trend to higher mortality rates than those without RLS.

Most studies show that the prevalence of RLS in ESRD is about 20% to 35%. Similar numbers were reported at APSS. Oka and colleagues from the Kyoto School of Medicine in Japan found that 28.7% of 41 patients on hemodialysis had RLS and Gillis and co-investigators from Henry Ford Hospital in Detroit showed that 25% of 737 hemodialysis patients met IRLSSG diagnostic criteria. In the Gillis study, only 8.1% of the sample had
been diagnosed with RLS and 2% were receiving treatment for the problem. This study illustrates what Winkelman considers a major challenge: to make nephrologists aware of RLS in their ESRD patients and provide treatment. Winkelman says that nephrologists consider RLS a quality of life issue, and may not appreciate that RLS may interfere with dialysis compliance.

Recognizing the four core URGE criteria may not be easy in these often older patients with ESRD who may also manifest chronic scratching, neuropathic pain, depression, and poor sleep hygiene. Winkelman suggests that a sleep study with PSG is appropriate for an ESRD patient with suspected co-morbid sleep disorder.

Treatment of RLS in patients with ESRD on hemodialysis has two aims: to relieve waking discomfort and consolidate sleep. Special treatment considerations are necessary since patients with uremic RLS may have worse symptoms than those with primary RLS and they cannot metabolize drugs through their kidneys.

Winkelman says he has seen progress in treating RLS in ESRD since the days when restless patients on dialysis were given haloperidol to calm them. Dopaminergic medications are considered the first-line treatment of RLS in ESRD patients, although there is no data available on the pharmacodynamics of these medications in ESRD. Double-blind studies have demonstrated that levodopa and carbidopa can improve RLS and decrease PLMS in ESRD. Caution should be used with pramipexole for people with ESRD since it is almost entirely excreted by the kidney. Ropinrole undergoes mostly hepatic metabolism.

If opioids are used, treatment should begin with short-acting agents, such as codeine, oxycodone, hydrocodone, or morphine, advised Winkelman. Agents with long-acting metabolites (meperidine, propoxyphene), which may not be cleared by dialysis or have increased half-life due to the patient’s anephric stage, should be avoided.

Some anticonvulsants can be used, alone or in combination with a dopaminergic or opioid, for RLS in ESRD. Gabapentin is cleared by dialysis but is eliminated only by the kidneys. Citing the risk of ataxia, Winkelman warns that any patient on gabapentin should discontinue gabapentin if a dialysis session is missed. Phenytoin, carbamazepine, and valproate are not effectively cleared by hemodialysis and should be used with caution in this population.

Supplementing iron is another approach to treatment of RLS in patients with ESRD, who may have iron deficiency due to chronic phlebotomies, dialysis-related blood loss and other problems. Winkelman believes that although many people with ESRD have problems with iron, he does not think iron deficiency is the sole etiology of RLS in these patients. Nonetheless, a recent study by Sloand suggests the IV iron dextran therapy may become a reasonable treatment alternative to standard RLS medications. Winkelman suggests that ESRD patients with severe RLS may benefit from a combination of IV iron and dopaminergic or other standard medications for RLS.

**RLS and PLMS in Children**

Experts at APSS advised that when it comes to RLS and PLMS, children should not be considered "little adults." Children with RLS or PLMS have different diagnostic criteria, are often more difficult to work up, and require different treatment strategies than adults with the same disorder.

It is generally accepted from the limited case reports and case series available that RLS and Periodic Limb Movement Disorder (PLMD) do occur in children. The prevalence is unknown, although Daniel Riccetti, MD, indicated that 1.2 million children in the United States have RLS, citing one study that showed 8.4% of a sleep clinic sample and 12% of a community sample had PLMD. About 35% of adults diagnosed with RLS report the onset of symptoms by age 20. Riccetti presented the results of a small unpublished study that suggested that there may be a time lag of several years between when a child is brought to a physician with clinical sleep disturbance without overt signs of RLS, and the eventual appearance of symptoms that meet RLS criteria.

**Diagnosis**

In 2003, diagnostic criteria for RLS and PLMD in children were published, describing the criteria necessary for definite RLS, probable RLS, possible RLS, and PLMD (Table 4). There are two ways to make a diagnosis of definite RLS in a child: with the first, the child must have all four URGE criteria that are necessary for diagnosis in adults, plus they must be able to describe the leg discomfort in their own words OR if the child cannot describe the discomfort in their own words, they must meet all four adult URGE criteria and meet two of three additional criteria (Table 4).

The first step in the diagnostic work-up of a child suspected of RLS is a thorough history; however, one of the first problems encountered is that a child usually cannot provide a good history. However, parents complain about interrupted sleep, affecting both the child and parents, although they usually deny that the child has nocturnal leg jerking. Children with RLS describe a variety of symptoms that may be confused with other disorders. Young children sometimes complain of RLS dyesthesias, using descriptions such as “itchy feeling, need to wiggle, ants on bottom of feet, feels funny, or my legs want to kick.” They indicate symptoms that are mild and intermittent, they deny the urge to move, and are not aware of nighttime worsening. Clinicians sometimes ascribe these feelings to growing pains, ADHD, or the possibility of sleep apnea. RLS must be differentiated from other causes of lower-extremity discomfort in children such as sore muscles, chondromalacia patella, Osgood-Schlatter disease, arthralgia, and cramps. Physicians should ask whether the child sits for prolonged times in awkward positions, which may cause aches and pains.
Table 4. Diagnostic Criteria for RLS in Children

- Definite RLS
  - 4 of 4 adult criteria and unpleasant sensations or
  - 4 of 4 adult criteria and 2 of 3:
    - Sleep disturbance for age
    - Family history of RLS
    - PLMS ≥ 5 per hour
- Probable RLS
  - First 3 of 4 adult criteria but not worse at night and
  - Family history of RLS
- Possible RLS
  - PLMD and
  - Family history of RLS
- Periodic Limb Movement Disorder (PLMD)
  - PLMS on PSG exceeding norms for age (≥5 per hour)
  - Clinical sleep disturbance for age (either sleep onset, sleep maintenance, or excessive sleepiness)
  - PLMS not secondary to:
    - Sleep-disordered breathing
    - Medications


Clete A. Kushida, MD, PhD, comments: We do know that RLS can occur in children. The problem with the diagnosis is that there are certain conditions that can mimic or be confused with restless legs syndrome. And they include conditions like attention deficit hyperactivity disorder, where the child appears irritable and has difficulty concentrating in the classroom. Now, the problem with it is that children with restless legs syndrome can also have those symptoms. And oftentimes, a child with restless legs syndrome might be misdiagnosed and be thought to have attention deficit hyperactivity disorder, instead of restless legs syndrome. Another condition is growing pains. Sometimes patients with bone problems might be felt to have growing pains as opposed to restless legs syndrome. So sometimes the pediatrician might not immediately think that the child might have restless legs syndrome instead of growing pains.

Often a sleep laboratory evaluation is appropriate for a child who may have RLS, especially if there is suspicion of a sleep-related breathing disorder. When a child is having PSG, technical adjustments may be required to assure accurate recording of PLMS (eg, left and right legs are recorded on separate channels, the sampling rate is high enough (≥256) to record activity, and there is sufficient sensitivity to record toe twitches). Children do not normally have PLMS; if PLMS are detected, clinicians should rule out causes such as medications (especially SSRIs) or narcolepsy, and consider RLS. Even if PLMS are detected, it is important to remember, as Barbara A. Phillips, MD, MSPH, commented, that in children as in adults, PLMS are neither necessary nor sufficient to make a diagnosis of RLS.

Measurement of serum ferritin levels may indicate iron deficiency as a contributing factor to the child’s RLS. There are no guidelines for the treatment of children for iron deficiency related to RLS. Picchietti suggests ferritin levels <25 mcg/L can be treated with oral iron for 2 to 3 months, while ferritin levels >25 but <40 can be managed with a multivitamin containing iron. Clinicians should be aware that ferritin is an acute phase reactant, so sampling while a child is ill may lead to falsely elevated readings, and that iron supplementation may take months before a clinical effect is detected.

Barbara A. Phillips, MD, MSPH, comments: Iron is related to RLS in children and adults, and we have treatment trials in adults that show that iron replacement can improve RLS symptoms in adults who have serum ferritin levels below 45 micrograms. In children the data are less clear, partly because we don’t have good norms or a good cut-off to decide when to initiate iron treatment in children. But clearly iron is important in the pathogenesis of RLS and I see no reason to think that this would be different between adults and children. But one important caveat that was brought out about measuring iron with the idea of replacing it in kids is that a child with an acute upper respiratory tract infection, for example, which is way more common in children than it is in adults, will have a spuriously elevated serum ferritin because ferritin is an acute phase reactant. In other words, if the child is sick that’s not the time to test the serum ferritin.

Treatment of RLS in Children

Barbara A. Phillips, MD, MSPH, comments: Since we do not have randomized placebo-controlled data about pharmacologic treatment of RLS in children with ADHD, and since we do not have a drug with an FDA indication to treat RLS in either adults or children, my personal preference will be to avoid pharmacologic treatment of RLS in children at present. I think Dr. Trenkwalder today espoused similar concerns about the use of any pharmacologic agent to treat women who are pregnant. I understand that RLS can cause difficult situations with impaired quality of life for children and pregnant women just the same as the rest of the population. But these are special situations and we tend to approach them more conservatively.

The goal of RLS treatment in children is to improve daytime function by achieving sleep quality and quantity appropriate for the child’s age. Experts generally discourage treating RLS in children if the goal is to control RLS
dysesthesia or assuage complaints by parents about their child’s or their own disrupted sleep. There are no set guidelines for the minimum age to treat a child with RLS or PLMS. Because of the difficulties associated with treating a child with RLS or PLMS, referral to a specialist is usually advised.

First steps appropriate for all children with RLS are to assure good sleep hygiene, including that the child is following a good age-appropriate sleep schedule. Intake of caffeine should be restricted. Ferritin levels should be checked and iron deficiency treated as described above.

There are no Level I studies on the treatment of RLS in children. If a specialist believes that medication is appropriate, clonidine is the most commonly used to treat the sleep problems associated with RLS in children, especially difficulties with sleep onset. Clonidine is generally well tolerated, with nightmares and sleep terrors occasionally seen. Clonazepam is also used to consolidate sleep in children. Physicians should be aware of paradoxical activation reaction in some children. Sometimes, a combination of these drugs is helpful: clonidine for sleep initiation and clonazepam for sleep maintenance.

Sleep specialists have also noted that dopaminergic medications are well tolerated in children with RLS, especially in those children with high frequency of PLMS. Studies have shown levodopa/carbidopa can reduce RLS symptoms, although 10% to 20% of children may develop nausea. The use of dopaminergics in children is generally discouraged, especially because no long-term safety data is available. Picchietti cautions that the activity pattern of pramipexole follows a “U-shaped” curve, so that dosing too high may have less benefit than a moderate dose. Physicians may have to address concerns expressed by parents that their child is receiving a drug given for Parkinson’s disease (PD) by explaining that there is no link between RLS and PD, but that medications that help PD patients have been shown to also help patients with RLS.

Other medications sleep specialists may prescribe to promote sleep in children include temazepam, zolpidem, gabapentin, and levetiracetam. Opioids should be avoided in children.

**RLS, PLMS, PLMD, and Attention Deficit Hyperactivity Disorder (ADHD)**

Philip M. Becker, MD, comments: I cannot say with certainty if it is important to treat PLMS in a child with ADHD. In my opinion, if you have arousing PLMS at night of more than 5 per hour and you address those with pharmacotherapy, there will be a fairly good chance that the child will have better attention, focus, and behavior during the daytime. My current supposition is that we will discover the same common pathway of the dopamine system and its regulation with nocturnal PLMS and daytime attentional problems. What is remarkable is that if 32% of children with ADHD have frequent PLMS, how few of them are being treated for their nocturnal problem.

The relationships between RLS, PLMS, PLMD, and ADHD remain unclear. Both RLS and ADHD are associated with restlessness, both respond to dopaminergic medications, and both demonstrate dopaminergic deficits on PET studies.

Walters, who has studied many children with these disorders, believes that RLS/PLMS are more common in children with ADHD, and that ADHD is more common in children with RLS. However, it is not clear why this is so. Picchietti found that 26% of 69 ADHD children had ≥ 5 PLMS/hr and 64% of 14 children with ADHD had ≥ 5 PLMS/hr.15,52 These children often had disrupted sleep, less sleep (by 43 minutes on average per night), difficulty falling asleep, and several awakenings per night. Picchietti and Walters found 15 of 16 children with PLMS ≥ 5/hr had ADHD and 4 had RLS15 while Crabtree et al15 reported 44.4% of children with PLMS ≥ 5/hr had ADHD. Walters says he has observed that children with severe RLS may become hyperactive when sitting in the classroom.

Walters said that treating children with PLMS and ADHD, with or without RLS, with dopaminergic medications helps both disorders. He is currently involved in a 4-site double-blind trial looking at this. He says methylphenidate can help relieve both RLS and ADHD symptoms, but its use for RLS at night is not pragmatic because its stimulating properties would disrupt the child’s sleep. At a symposium on PLMS in children, Jane Gaultney, PhD, of the University of North Carolina at Charlotte discussed unpublished data that indicated that hyperactivity is associated with PLMD, while sleep problems and poor cognitive function are more likely to reflect sleep-disordered breathing. She says that treating sleep-disordered breathing, for example with CPAP, may improve sleep and cognition, but not hyperactivity.

What is clear is that the presence of co-morbid conditions like RLS or ADHD in children who may also have frequent PLMS, sleep difficulties, and cognitive and behavioral problems presents considerable diagnostic and treatment challenges. Referral to a pediatric neurologist or sleep specialist may be appropriate for these patients.

**Summary**

Barbara A. Phillips, MD, MSPH, summed up why RLS was the focus of so much attention at APSS: Ten years ago, RLS was in the category of rare diseases and not many clinicians knew about it. If they knew about it, they did not know what caused it or how to treat it. There has been a very gratifying explosion in our knowledge about this disorder and how it affects the lives of patients. This is a condition for which effective therapies are now available that can totally affect the life of a patient for the better. So, I think people are here because finally we are beginning to understand the pathology of RLS and we have specific treatments, the dopaminergic agents, that don’t just mask the symptoms—they actually treat the underlying mechanisms.
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Societies (APSS) Annual Meeting
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News and Views from the AUDIO CD

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References
18. Monplaisir J, Michaud M, Deneau R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Mov Disord. 2001;16:165-176.


For additional information on neurology, go to www.projectsinknowledge.com

All 5 parts of this CME series are available at www.projectsinknowledge.com/RLS-NewsViews/
CME Posttest

Expert Perspectives in Restless Legs Syndrome: News and Views from the 2004 Associated Professional Sleep Societies (APSS) Annual Meeting

CME Instructions

To receive CME credit for your participation in this CME activity, please complete the following steps:

2. Read both 2-page faxes, and the daily (June 7–10) web postings (brief audio clips and written highlights about each day’s RLS events)
3. Read this Tx Reporter newsletter and listen to the accompanying audio CD.
4. Complete the CME Posttest below, selecting the most appropriate response to each question.
5. Complete the CME Evaluation Survey (please be sure to indicate how long it took to complete this activity).
6. Send photocopies of the Posttest and Evaluation to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424, or fax to: 973-890-8866 by August 31, 2005. Please note that we cannot issue certificates of CME credit without both documents.

If you complete these steps and score 70% or higher, Projects In Knowledge will mail you an acknowledgment of participation within 6 weeks of receipt of your materials. If you score lower than 70%, you will be notified by mail and given another opportunity to retake the test.

Name __________________________________________________________________ Degrees/Credentials ________________

Mailing Address ______________________________________________________________________________________________

City _____________________________________________________________________ State ________ ZIP ________________

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Please select the most appropriate response to each question.

1. Each of the following are known risk factors for RLS, except:
   a. Age
   b. Gender
   c. Heredity
   d. Trauma

2. Most studies report RLS prevalence in Western general adult populations to be approximately:
   a. 2%
   b. 10%
   c. 30%
   d. 50%
   e. 80%

3. Which of the following is necessary to make the diagnosis of RLS?
   a. Clinical history
   b. Polysomnography
   c. Ferritin levels <17 mcg
   d. Symptoms occurring more than 3 times a week

4. All patients with RLS also have periodic limb movements of sleep.
   a. True
   b. False
5. A patient complains of discomfort in her legs that is not relieved by movement and worsens in the early morning hours. What is the most likely cause of her symptoms?
   a. RLS
   b. Neuroleptic-induced akathisia
   c. Peripheral neuropathy
   d. Nervousness

6. Patients with RLS may complain of:
   a. Unrelenting urge to move, especially at night
   b. Difficulty in falling asleep and staying asleep
   c. Concentration difficulties
   d. Depression
   e. All of the above

7. The most useful diagnostic test for evaluating iron deficiency in a patient with RLS is measuring levels of:
   a. Hemoglobin
   b. Ferritin
   c. Transferrin
   d. TIBC
   e. Serum iron

8. Which class of drugs is generally considered first-line treatment for idiopathic RLS?
   a. Opiates
   b. Anticonvulsants
   c. Dopaminergic agents
   d. Sedative-hypnotics
   e. Antihistamines

9. If a patient develops symptoms of augmentation while taking a dopamine agonist, what should the clinician not do:
   a. Lower the dose of the dopaminergic agent
   b. Raise the dose of the dopaminergic agent
   c. Give an earlier dose of the dopaminergic agent
   d. Switch to an opiate
   e. Switch to a dopaminergic agent with a longer half life

10. A patient with RLS who is depressed has been taking the SSRI fluoxetine, but comes into your office complaining of worsening leg movements at night. What should you do?
    a. Raise the dose of fluoxetine
    b. Consider switching the patient to another SSRI such as sertraline
    c. Consider switching the patient to a tricyclic antidepressant such as imipramine
    d. Consider switching the patient to bupropion

11. A patient on hemodialysis due to end-stage renal disease develops RLS. Which medication may be preferred because of its efficacy and hepatic metabolism?
    a. Propoxyphene
    b. Ropinirole
    c. Pramipexole
    d. Clonazepam
    e. Gabapentin

12. Which medications have been approved to treat children with RLS?
    a. Dopaminergic agonists
    b. Opioids
    c. Anticonvulsants
    d. Sedative-hypnotics
    e. None of the above

Thank you for your participation.
Expert Perspectives in Restless Legs Syndrome: News and Views from the 2004 Associated Professional Sleep Societies (APSS) Annual Meeting

Name __________________________________________ Degrees/Credentials _______________________________

Address ___________________________________________________________________________________________________

City __________________________________________ State _______________ ZIP _______________________

Instructions: Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8866. We cannot issue certificates of CME credit without both documents.

1. Please rate the extent to which you achieved the learning objectives:

   - Incorporate the latest data on RLS epidemiology, and genetics and other risk factors, into identification and diagnosis of patients at risk for the disease.
     Excellent Very Good Good Satisfactory Poor
     ❑ ❑ ❑ ❑ ❑

   - Differentiate between RLS and other disorders such as peripheral neuropathy based on clinical presentation and the results of polysomnography.
     Excellent Very Good Good Satisfactory Poor
     ❑ ❑ ❑ ❑ ❑

   - Identify RLS in special populations, including children, pregnant women, and patients with other conditions such as ADHD.
     Excellent Very Good Good Satisfactory Poor
     ❑ ❑ ❑ ❑ ❑

   - Formulate diagnosis and treatment strategies for patients with co-morbid disease.
     Excellent Very Good Good Satisfactory Poor
     ❑ ❑ ❑ ❑ ❑

   - Develop an effective RLS treatment plan based on safety and efficacy data of available therapies.
     Excellent Very Good Good Satisfactory Poor
     ❑ ❑ ❑ ❑ ❑

   - Translate an understanding of the latest data on RLS pathophysiology into selection of appropriate treatment strategies.
     Excellent Very Good Good Satisfactory Poor
     ❑ ❑ ❑ ❑ ❑

2. Please rate the extent to which this activity achieved the stated goal.

   The goal of this activity is to provide clinicians with the key clinical data and insights on the diagnosis and treatment of RLS from the APSS Annual Meeting.

   Excellent Very Good Good Satisfactory Poor
   ❑ ❑ ❑ ❑ ❑

   Strongly Agree Agree Disagree Strongly Disagree

3. Course was free from commercial bias:

   If you “Disagree” or “Strongly Disagree,” why?....................................................................................................................................................
   ..................................................................................................................................................................................................................................

4. Please rate the level of the material presented:

   ❑ ❑ ❑ ❑ ❑

5. Please list any changes in your practice that you would consider making as a result of participating in this activity:

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6. Please rate your interest in self-directed or distance learning in the following formats:  Very Interested  Moderately Interested  Not Interested
   a. Audioconference
   b. Videoconference
   c. Enduring materials (audio CDs, videotapes, monographs)
   d. Internet (online discussions with experts, educational activities)
   e. Multimedia (online, CD-ROM)

7. Please tell us exactly how long it took you to complete the newsletter (circle hours and minutes):
   Hours: 0 1 2 3  Minutes: 0 15 30 45

8. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

9. Follow-up:
   As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:
   ☐ Yes, I would be interested in participating in a follow-up survey.
   ☐ No, I’m not interested in participating in a follow-up survey.

10. Additional comments about this activity:

Thank you for your participation.