



Restless Legs Syndrome: A Case-Based Review

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the prevalence and impact of restless legs syndrome (RLS)
- Identify risk factors or conditions that are associated with RLS
- Individualize behavioral and pharmacologic treatment plans for patients with RLS
- Identify 3 different perspectives on RLS: primary care, psychiatry, and neurology

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Dr. Brunton has participated in advisory boards for Abbott Laboratories, Allergan, Amylin Pharmaceuticals, Bristol-Myers Squibb, Novo Nordisk, sanofi-aventis, U.S., and Sciele Pharma.

Dr. Earley has nothing to disclose.

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This case-based review includes discussion of unlabeled/unapproved uses of benzodiazepines, opioids, and alpha-2-delta calcium-channel modulators.

CME Information

Presented by The Johns Hopkins University School of Medicine.

This activity is supported by an educational grant from GlaxoSmithKline.

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Program Release: February 2010

Program Expiration: February 2011

Estimated time to complete: 70 minutes

There are no prerequisites for participation.

The intended audience for this CME case study includes all clinicians who treat patients (pediatric, adult, and elderly) with sleep disorders. This includes all primary care specialties, pediatricians, neurologists, psychiatrists, pain specialists, obstetricians-gynecologists, physician assistants, and nurse practitioners.

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This activity consists of an interactive case study commentary. To participate in this activity, please review the course materials and complete the CME quiz.

Restless legs syndrome (RLS) is a sleep disorder characterized by an irritating, overwhelming urge to move the legs that occurs at bedtime. RLS is common in both adults and children and is estimated to affect 2.5% to 10% of the population, including approximately 10 million adults and 1.5 million children in the United States.¹ To increase awareness of the real-world challenges associated with the diagnosis and management of RLS, Sleep University CME invited clinicians to submit a case study discussing one of their most clinically challenging patients with suspected or confirmed RLS.

The Sleep University CME faculty selected one submission among several excellent cases and prepared a thoughtful commentary in response to the questions raised within the chosen case.

CASE STUDY

Identifying Information

The patient is a 93-year-old woman with a history of “a terribly uncomfortable sensation in my arms and legs at night.”

History of Present Illness

The patient initially presented to her primary care physician about 3 years ago due to very uncomfortable sensations and difficulty falling asleep. At that time she described several occasions, occurring a few months apart, when she suddenly felt overcome at bedtime by an indescribable and exquisitely uncomfortable feeling in her arms and legs that was relieved only by pacing. She would get out of bed and pace for hours until she was so exhausted that she finally would be able to sleep. The distressing sensation would be gone when she awoke in the morning. Initially, several months would pass before she'd have another episode. Each occurrence was so upsetting to her that she described living in fear of the next episode. Her medical history included chronic back pain for which she was prescribed narcotic analgesics (fentanyl and oxycodone). She wondered whether her episodes were related to opiate withdrawal, because they seemed to occur when there was a delay in the replacement of her fentanyl patch.

The patient was referred by her primary care physician (PCP) to a pulmonologist specializing in sleep disorders due to the suspicion that RLS might be the cause of her problem. The pulmonologist agreed with the RLS diagnosis and recommended that she take ropinirole (Requip®) 1 mg at bedtime. He also suggested that she take an additional .5 mg every 15 minutes as needed in the event of a restless legs episode. This regimen offered no improvement in the frequency of episodes. The dose was gradually increased to the point where the patient was taking ropinirole doses of 3 mg at bedtime and 1 mg every 15 minutes as needed for an acute episode. Over time, the frequency of the episodes increased and ultimately occurred every few weeks.

During this same period, the patient's narcotic regimen was also slowly increased, from a 25- μ g fentanyl patch and oxycodone 5 mg every 8 hours as needed to a 200- μ g fentanyl patch and oxycodone 5 mg every 4 hours as needed. Despite this increase in the narcotics doses, she experienced no further relief of her chronic back pain or of her restless legs symptoms. The patient's PCP also prescribed a series of hypnotic agents, including zolpidem and zaleplon, which he instructed her to take in the event of a restless legs episode. These agents did not help her to fall asleep more quickly, and she fell on several occasions after resuming her pacing.

The patient reported that on nights when she did not experience a severe restlessness episode, she would fall asleep without difficulty and sleep soundly throughout the night. She usually took a shower at around 9 pm and then had a small snack before getting into bed. She read in bed until falling asleep around 10:30 pm. She would sleep through the night and awaken in the morning at around 6:30 am. She said that over the past few years she had experienced an increasing need to nap in the afternoon. Her family members observed that over the past year she had started falling asleep repeatedly throughout the day, sometimes even in the middle of conversations.

The family also had observed some patterns related to the patient's restless legs episodes. Initially the episodes were more likely to occur on nights when she was exhausted—for example, after staying up late having an emotionally taxing phone conversation with her daughter in California. Later the episodes seemed more likely to occur when she was dehydrated and constipated. This occurred most frequently after an increase in the dose of her fentanyl patch, which resulted in nausea, constipation, and dehydration. She then would have a particularly severe episode of evening restlessness. Several years ago she also experienced an episode as the result of dehydration from gastroenteritis. A family member who witnessed this episode said that one of the patient's arms seemed to be jerking intermittently throughout the evening, and she seemed to be “speaking in tongues.”

About 2 months prior to the current evaluation, the patient had been referred a second time by her PCP to the pulmonologist who had

diagnosed her with RLS. He recommended the addition of clonazepam .5 mg as needed for episodes of restless legs. In the subsequent 28 days, the patient took 17 tablets of clonazepam .5 mg but later had no memory of ever taking it.

Three weeks before the current evaluation, the patient was hospitalized for 5 days due to nausea, vomiting, constipation, and dehydration. She was diagnosed with opioid-induced ileus and near obstruction from obstipation. Upon admission, the patient's fentanyl patch dose was reduced from 200 µg to 100 µg every 72 hours. While in the hospital, she experienced nightly episodes of severe restlessness. Her ropinirole dose was increased from 3 mg at bedtime to 4 mg without any additional relief. On hospital day 4, a standing dose of clonazepam .5 mg was initiated, and the patient was finally able to sleep through the night. Because ropinirole had provided no relief for her restless legs symptoms, it was discontinued on the day of discharge. Zaleplon, which had also failed to provide relief of her symptoms, was discontinued several days following discharge.

The patient was evaluated 2 weeks after discharge from the hospital. She had been on clonazepam .5 mg at bedtime since her hospitalization and continued to sleep soundly through the night. She had experienced no recurrences of restless legs symptoms, but she remained quite fearful of a recurrence and asked for help in preventing further episodes.

Past Medical History

- Renal insufficiency with a baseline creatinine of 1.4 mg/dL
- Myelodysplastic syndrome
- Severe osteoporosis complicated by multiple vertebral compression fractures
- Severe kyphosis, scoliosis, and degenerative changes of the thoracic and lumbar spine status post-lumbar fusion and laminectomy
- Chronic back pain
- Hypertension
- Macrocytic anemia (with no evidence of iron deficiency)
- Left lower extremity deep venous thrombosis status after placement of Greenfield filter
- Right thumb arterial embolus 5 years prior
- Bilateral lower extremity lymphedema
- Bilateral hearing loss

Medications

- Furosemide 40 mg po daily
- Enalapril 5 mg po bid
- Ferrous sulfate 325 mg daily
- Ergocalciferol 50,000 units po daily
- Docusate sodium 100 mg bid
- Lactulose 30 mL po daily
- Polyethylene glycol 17 g po bid
- Clonazepam .5 mg po qhs

- Fentanyl patch 100 µg q72 hours
- Oxycodone 5 mg po q8 hours
- Glucosamine sulfate 1500 mg po daily
- Potassium chloride 20 mEq po daily
- Lansoprazole 30 mg po bid

Medication Allergies

None known

Family History

The patient's father died at age 40 from infective endocarditis. Her mother died at age 94 from pneumonia. She has no siblings. There is no known family history of sleep disorders.

Social History

The patient was living independently in a retirement community until her recent hospitalization, when she was transferred for subacute care in a nursing facility. She was widowed 15 years ago after 55 years of marriage. She has 3 living children in their 60s. A daughter died at age 26 from complications of anorexia nervosa. She has never smoked and has no history of illicit drug use. She drinks an occasional glass of wine at social gatherings, and her caffeine consumption consists of no more than 1 cup of coffee daily.

Physical Examination

- Vital signs:
 - T 36
 - R 12
 - BP 152/79
 - HR 56
 - O₂ sat: 94% on room air
 - Wt 100 lbs
- General: Frail, thin elderly woman with severe kyphosis and scoliosis, in no acute distress; ambulates with a walker
- Lungs: Clear to auscultation bilaterally
- Heart: Regular rate and rhythm. No murmurs, rubs, or gallops
- Abdomen: Soft, nontender, nondistended. Normal bowel sounds
- Extremities: Heberden's and Bouchard's nodes in the hand joints bilaterally. Nonpitting edema in the lower extremities bilaterally

Mental Status Examination

The patient has good eye contact and is fully cooperative with the exam. Her attention fluctuates throughout the exam, and she shifts her position repeatedly in an attempt to be more comfortable. Her speech is fluent, spontaneous, and goal directed, although she often has trouble hearing the examiner's questions and at times misinterprets them. She describes her mood as "good," and her affect is full. She denies symptoms of depression or anxiety. She denies suicidal ideations or hallucinations. No delusions are elicited. She is fully oriented.

FACULTY RESPONSE

Sleep University CME thanks Amy Huberman, MD, Johns Hopkins Hospital, Baltimore, MD, for submitting this very interesting case for review. This case study and expert faculty response highlight several key aspects of the evaluation and management of RLS.

The faculty commentary that follows highlights several themes that were derived from questions submitted about this case. The case response reviews:

- Symptoms of RLS
- Factors influencing RLS
- Causes of RLS
- Typical course of RLS
- Differential diagnosis
- RLS treatment strategies and considerations

Additionally, the case study underscores the importance of integrated care and an improved understanding of RLS by primary care providers, psychiatrists, and sleep specialists in improving health outcomes for people with RLS.

Brief History of RLS^{2,3}

The constellation of symptoms that we describe as RLS has been mentioned in writings going back for hundreds of years. In 1695, Thomas Willis wrote, “Wherefore to some, on being a bed, they betake themselves to sleep, presently in the arms and legs, leaping 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 the place of the greatest torture.”

Similarly, in 1880 George Beard in describing neurasthenia wrote, “Fidgetiness and nervousness, inability to keep still—a sensation that amounts to pain—is sometime unspeakably distressing. When the legs feel this way, the sufferer must get up and walk or run, even though he be debilitated and is made worse by severe exercise.”

The modern era of appreciating RLS as a syndrome with distinct characteristics and causes began with Karl Ekbom’s work in the 1940s. He discussed the problem of irritable or restless legs occurring when one was at rest and the temporary relief that is achieved with movement. He also noted associations with iron deficiency and pregnancy.

Symptoms of RLS

In our case presentation, the patient described feeling “overcome at bedtime by an indescribable and exquisitely uncomfortable feeling in her arms and legs that was relieved only by pacing.” Is this consistent with RLS?

RLS is characterized by 4 essential criteria and several possible associated features.⁴

The core feature of RLS is a strong and uncomfortable urge to move that is temporarily relieved with activity. The symptoms worsen in the evening and occur primarily when the person is at rest.

A mnemonic to remember these 4 criteria is URGE:

- **U**rge to move
- **R**est induced
- **G**ets better with activity
- **E**vening and night accentuation

The urge to move is an unpleasant sensation that most typically is felt in the legs but may generalize to the arms or other parts of the body. Patients may describe it as an overwhelming “creepy-crawly” or “tingly” sensation, or perhaps simply as “hard to describe.” Often they also report that the urge to move is irresistible and uncontrollable. A crescendo in the urge results in a voluntary or involuntary movement followed by only a brief period of relief. The abnormal sensation is probably best characterized as a focal or segmental akathisia.

The sensory and motor symptoms of RLS generally start or worsen while a person is at rest, especially while sitting or lying down. The symptoms are more likely to occur during periods of inactivity especially when the person feels increasingly more comfortable. A decrease in mental activity or focus also may contribute to the risk for the development of the RLS symptoms.

The uncomfortable RLS sensations should be significantly relieved with motor activity (eg, walking). The relief should be rapid and continue as long as the person is physically active. To some degree, focused mental activity also may help relieve the physical sensations. In some cases, leg rubbing and hot or cold baths can serve as counter stimuli to offer some relief.

Finally, the symptoms follow a circadian pattern, with worsening during the evening, although for some individuals the disease progresses with an onset of symptoms earlier in the daytime. Generally the morning is a protected time.

Factors Influencing RLS

Our patient seems to have chronic difficulty with her sleep that is much worse on her restless nights. Sometimes she is up for hours pacing. She most recently was taking nightly clonazepam and she previously had been prescribed various hypnotics.

Patients with RLS often complain of difficulty falling asleep and remaining asleep. Physicians should consider RLS in the differential diagnosis of sleep-onset insomnia. Upon awakening, patients with RLS may or may not experience the sensory symptoms. The usual reason for awakening is the presence of rhythmic or semirhythmic movements of the legs during sleep (periodic leg movements of sleep, or PLMS), which typically will abate with awakening. Approximately 85% of RLS patients experience PLMS.^{5,6} As a consequence of the sleep disruption, RLS patients may experience chronic sleep insufficiency and related daytime complaints. The sleep history can be a useful tool during therapy.

The patient and her family said that her RLS tended to be worse when she was exhausted and after late-night emotional family telephone conversations. Could these situations have played a role?

Emotional reactions per se do not seem to worsen RLS, but sleep loss definitely plays a role.

Our patient is 93 years old and has had the RLS symptoms for just a few years. Is age an important factor regarding the development of RLS?

The prevalence and severity of RLS increase with age.⁷ Symptoms have been reported as early as 3 to 4 years of age and as late as the 90s. The etiology may vary in different age groups. People with symptoms starting later in life are more likely to have associated anemia, peripheral neuropathy, myelopathy, neurodegenerative conditions, and renal insufficiency. These conditions may represent secondary cases of RLS. Onset in early adulthood more likely represents primary RLS.

Does the fact that our patient is female and has given birth to 3 children affect the likelihood of her developing RLS?

The prevalence of RLS in females is twice that of men across all ages⁸; however, in early onset RLS the prevalence of RLS is 3 times that of men.^{8,9} Late-onset RLS is less associated with gender.⁷

The prevalence of RLS increases during pregnancy across the trimesters, reaching 25% to 30% during the last trimester.^{10,11} For the majority of pregnant women who experience RLS, such de novo symptoms resolve at the time of delivery. Recent findings demonstrate that RLS risk increases with a woman's number of pregnancies.¹² The increased gender risk of RLS may be driven by the risk associated with pregnancy.¹²

Our patient had no family history that included symptoms of RLS. Is that common?

The overall RLS prevalence is reported to be between 2.5% and 10%.^{7,13} Patients with idiopathic RLS are likely to have a family history of RLS.¹⁴ Among people older than 65 years of age, the peak prevalence is about 6% for woman and about 3% for men.⁷ Among people in their 20s, the prevalence is about 1% to 1.5%.⁷

There have been gene-wide association studies performed by 3 independent research groups that have identified 5 genes associated with increased risk for RLS.^{15,16} About 80% to 85% of the risk of developing RLS can be attributable to 2 of the genes: *MEIS1* and *BTBD9*.¹⁷ Currently, the relationship of these genes and the underlying pathophysiology of RLS are unclear. Genetic testing currently has no role in the diagnosis or management of RLS; however, it still may be performed for research purposes.

Our patient experienced episodes of dehydration. Is dehydration known to worsen RLS?

At the present time there is no reason to believe that dehydration worsens RLS.

Typical Course of RLS

Our patient initially experienced her distressing episodes of restlessness several months apart, although she seemed to live in nightly fear that they would return. Is her history unusual?

There are several typical courses of RLS. Young adults initially tend to have occasional and intermittent RLS symptoms, but over 20 to 30 years

they develop nightly symptoms and an increased level of severity. Older individuals often develop symptoms progressing over a period of weeks to months with nightly symptoms and maximum severity being experienced within 1 to 2 years. Some patients, both young and old, have infrequent and mild symptoms that persist at this level without developing further in severity or frequency.

Causes of RLS

In the case presented here, it seems that RLS was diagnosed because of the patient's symptoms. But in other patients, the diagnosis may not be as clear. What possible causes could be considered to help determine a diagnosis?

The Role of Iron in RLS

Iron deficiency is the single largest risk factor for RLS, and treating the iron deficiency is associated with a resolution of the symptoms. However, even with a normal blood level of iron, studies have shown that brain stores of iron are lower in RLS patients. The etiology of the brain iron deficiency in those with otherwise normal blood levels of iron is not clear. The effects of low brain iron—for whatever reason—appear to have an affect on the dopaminergic system, and this affect may play a central role in the development of symptoms. Studies have shown that iron is important for dopamine synthesis and for dopamine transport and receptor functioning.

A wide variety of laboratory measures are often employed in the evaluation of anemia. The best measure of body iron stores is a bone marrow biopsy. The next-best measure is serum ferritin, as it is most sensitive to a wide range of changes in body iron stores. It is, however, an acute-phase reactant and can be falsely elevated at any level of inflammation and shows progressive increases above normal in the elderly even without clear evidence of inflammation. The usual laboratory ferritin normative range is from 10 µg/L to 300 µg/L; however, based upon bone marrow results, patients with ferritin levels of 20 µg/L have an 85% chance of iron deficiency, and patients even with 50 µg/L and anemia have a 6% to 7% chance of having iron deficiency. These data do not take into account the consequence of aging on the ferritin level; thus, in a 90-year-old person, a ferritin level of 80 µg/L easily could be associated with an iron deficiency.

Renal Function and RLS

The prevalence of RLS among patients on hemodialysis is about 30% to 40%.¹⁸ This rate has been remarkably improved with the more aggressive use of erythropoietin and iron infusion, thus implicating underlying iron metabolism issues in the development of RLS in dialysis patients. Renal transplant and a resumption of normal renal function in patients who did not have RLS prior to the renal failure usually results in a complete resolution of the RLS symptoms.

Worsening Due to Medications

Medications that may aggravate or trigger RLS symptoms include antidopaminergic medications (antipsychotics and antiemetics), antidepressants (with the exception of bupropion and trazodone), and antihistamines.⁶ For some patients, RLS symptoms may develop or worsen soon after initiating or after 3 to 6 months of chronic use. Symptoms usually abate with discontinuation of the offending medication, but a full resolution may take several weeks to a month to occur. RLS symptoms also may worsen when patients discontinue

Iron Supplementation and Considerations for Elderly RLS Patients

RLS patients with low serum ferritin levels may see symptoms improve by increasing iron stores in the body through oral or intravenous iron treatments. Iron is best absorbed when taken on an empty stomach and when there is an acidic nature to the stomach. Since the elderly tend to have a reduced stomach acidity or to take acid reducers, the iron should be given with vitamin C. Standard iron formulation is iron sulfate 325 mg. There are different formulations of iron that may be gentler on the stomach, but they tend to cause some degree of constipation and, in a few patients, diarrhea. A particular problem in the elderly is that the presence of any inflammation, even at a low level, is going to lead to a general decrease in the absorption of iron, in which case oral iron at any dose is of little value. The alternative is intravenous iron, which is approved for use in iron-deficiency anemia; the newer formulations generally are safer and pose a lower risk than the older formulations.

medications that have had therapeutic effects on their RLS. These medications potentially could include dopamine agonists, opioids, and benzodiazepines.

Our patient was prescribed a fentanyl patch for her back pain. Is it conceivable that our patient's use of the fentanyl patch had beneficial effects on her RLS symptoms and that there might have been a worsening of her symptoms on discontinuation?

The opiates are effective treatment for RLS. The worsening of the RLS symptoms with removal of the patch would be consistent with the notion that the fentanyl patch was actually helping the RLS symptoms.

Differential Diagnosis of RLS

In our case presentation, the sleep specialist diagnosed RLS and prescribed a medication. How should one begin the differential diagnosis of RLS?

The first and foremost diagnosis to consider is drug-induced akathisia, muscle or joint pain or discomfort that is worse at night, which includes arthritic pain, myopathy or myositis, or dependent leg edema causing discomfort. Pain in general complicates the ability to determine whether the patient is experiencing RLS or pain. RLS diagnosis and treatment become more challenging in the presence of any painful comorbidity. Leg cramps are common and typically have no association with RLS; but because of the frequent leg movements during sleep that occur with RLS, patients can experience more problems with leg cramps. Thus, treating the RLS and eliminating the PLMS can markedly improve the leg cramps.

RLS Treatment Strategies and Considerations

The use of various medications at different doses and at different times represented the treatment for the patient in our case presentation. Please describe the role of sleep hygiene and other nonpharmacologic approaches.

Standard approaches to sleep hygiene promote relaxation and comfort, but for RLS patients these behaviors may trigger the symptoms. While good sleep hygiene usually is good for most people, for RLS sufferers it may lead to more sleep loss. For example, some patients with moderate RLS will find it easier to sleep on a hard floor than on a soft, comfortable bed. Nonpharmacologic treatments include anything that increases sensation, such as hot showers, vigorous rubbing of the legs, or mild leg exercise like riding a stationary bike. All of these activities will immediately relieve the symptoms and may allow the patient to get to sleep before the symptoms arise again. However, these activities typically will not solve the problem for most patients. Therefore, the primary treatment options are mostly pharmacological.

The patient in our case presentation may not have received optimum treatment with the dopamine agonists. Her dosage was administered at bedtime, not prior to the usual onset of her symptoms. Further, she was taking multiple repeated doses with a relatively high total amount. How could the pharmacologic strategies have been optimized for our patient?

Dopamine Agonists

The FDA has approved 2 dopamine agonists—pramipexole (Mirapex®) and ropinirole (Requip®)—for the treatment of RLS. It was a serendipitous finding in the 1980s that carbidopa/levodopa (Sinemet®) brought about a complete resolution of RLS symptoms in all of the patients treated. Following from this finding was the development of clinical trials for the use of the dopamine agonists for the treatment of RLS. It was presumed that the addition of a dopamine precursor or receptor agonist would correct abnormally low dopamine activity associated with the development of RLS. Pramipexole and ropinirole both require at least 2 hours to reach peak effect on an empty stomach and therefore should be given 2 hours prior to the usual time of symptom development. Ropinirole has a half-life of about 5 hours, and pramipexole has a half-life of about 8 to 12 hours. Because pramipexole clears renally, in the elderly population with decreased renal function there is an increase in the half-life; thus, it is a longer-acting agent than ropinirole. Generally the dopamine agonists work best when used as a daily treatment, not on an as-needed basis.

The single biggest problem associated with use of dopamine agonists is the development of RLS augmentation, which is seen as apparent and progressive worsening of the symptoms.

Case Example

A patient takes a single dose at bedtime for symptoms. Eighteen months after treatment has started, he reports that his symptoms are now occurring earlier in the evening, so an earlier-evening dose is started with a resolution of symptoms. Nine months later the patient returns with afternoon symptoms, and the bedtime dose may not be holding so well. Further increases in the total dose will bring about improvement in symptoms, but the patient will continue to show progression of symptoms earlier and tolerance to the medication in the evening over a progressively shorter and shorter period. Symptoms will

become significantly more severe and debilitating, and the patient will develop anxiety about coming off of the drug.

The solution to the problem is to limit the treatment to the initial dose plus a one-time increase. Once the symptoms start to show progress, moving to alternate medications is recommended.

Late in the course of treatment, one may find side effects developing that may limit further use of the dopamine agonists. These effects include daytime sleepiness, sometimes at a level seen only in narcolepsy patients, and increased compulsive behaviors (buying, gambling, eating, etc).

Opioids

The opiates were among the first medications to demonstrate a significant benefit to RLS symptoms, but they were superseded by findings from the dopaminergic agents. None are presently approved by the US Food and Drug Administration (FDA) for the treatment of RLS. There is no clear indication that the dopaminergic agents are more effective than the opiates, but substantially more money has been invested in research on the dopamine agonists. There is no known scientific basis to the empirical findings regarding the opioid efficacy. There is also no indication that the opiates produce progressive worsening or augmentation of the RLS symptoms, as seen with the dopamine agonists.

Generally, if dopamine agonists fail or augmentation develops, opiates can be considered as alternatives. If the patient has coexisting problems with pain because of a neuropathy or arthritic issues, than the use of opiates may have a dual effect of improving the RLS and the pain.

Drugs in the codeine class are all relatively short-acting with half-lives of 3 to 4 hours. These drugs may be adequate if the evening symptomatic period is only 4 to 5 hours. If symptoms last longer than 6 hours, using bid dosing with codeine products (ie, oxycodone, hydrocodone, or codeine) or a long-acting agent (ie, OxyContin®, MS Contin® [8- to 10-hour half-life], methadone [16- to 22-hour half-life], or fentanyl patch [72-hour usage]) can be considered.

Sedation, constipation, and depression may occur with the use of opioids. High doses of any opiates may precipitate central sleep apnea, which may be expressed as increasing insomnia or daytime sleepiness. Methadone has been associated with cardiac arrhythmias at doses above those commonly used for RLS. The usual total dose for methadone is 20 mg or less compared with 100 mg or more associated with arrhythmias.

Alpha-2-Delta Calcium-Channel Modulators

The medications in this category are gabapentin and pregabalin. Studies have demonstrated benefits in the treatment of RLS patients.¹⁹⁻²¹ They can be used as primary treatment or after the failure of other agents, or in combination with a dopamine agonist or opiate agent. They are also a good primary treatment choice in people with pain-related conditions in the legs that coexist with RLS. These medications are not approved by the FDA for the treatment of RLS. A patient should take one dose 1 to 2 hours prior to usual symptom onset. If symptoms occur only at bedtime, then the patient should need only a single dose. Sedation and ataxia in the elderly can complicate a patient's efforts to walk around at night. Because of renal clearance, the

elimination half-life may be prolonged among the elderly when there is renal insufficiency.

Our patient currently is prescribed clonazepam at bedtime, and she previously had been given various benzodiazepine receptor-agonist hypnotics. Although not FDA approved for treating RLS, might they have a role in a patient's treatment?

Benzodiazepines

Benzodiazepines may have 2 roles: primary treatment and use in combination with other agents. People with mild symptoms, which may occur at bedtime and only a few days per week, may do well with a short-acting hypnotic. Once symptoms are severe and nightly, often the hypnotics alone are less likely to be effective and may even exacerbate symptoms. The side effects of dopamine agonists may include insomnia, which can be treated with the use of a short-acting hypnotic. The single biggest caution with benzodiazepines and related medications is the potential for excessive sedation and ataxia when RLS patients remain awake and out of desperation are walking to attempt to relieve their restlessness. There may be an increased risk of falls in this circumstance. Memory difficulty may be an additional concern, especially in elderly individuals.

Serial compression treatment has been reported to improve RLS. Is this a recommended treatment?

Several studies do suggest that serial compression treatment may be of value, but the methods and design to prevent experimental unblinding and the strong placebo have been inadequate.^{22,23} These studies use symptom responses and not objective indicators, such as total sleep time or PLMS. Prior studies with the dopamine agonists demonstrate a strong placebo effect, so more research is necessary to differentiate the actual placebo and experimental effects.

RLS Primary Care Perspective

Stephen A. Brunton, MD



It is important for primary care providers (PCPs) to think about RLS because it is common, causes significant distress to sufferers, is underdiagnosed, and is treatable.

Despite the high prevalence of RLS and the significant distress it causes to patients, it commonly goes undiagnosed in primary care. Sleep disorders are underdiagnosed mainly because patients fail to report symptoms to their physicians, and physicians do not routinely screen for sleep problems. Because patients with sleep disorders are most likely to visit their PCPs, either for acute medical conditions, chronic medical conditions, or routine physicals, it is particularly crucial for PCPs to be aware of the importance of screening. PCPs need to be aware of the association between RLS and iron deficiency. Because some people who have iron-deficiency anemia develop RLS, PCPs are in a position to recognize these symptoms and intervene early. Patients with RLS or other sleep disorders may describe themselves as tired, fatigued, lacking energy, or feeling down, without actually stating that they have not been sleeping well. The challenge lies in getting from such chief complaints to the RLS diagnosis. Through

use of a few simple screening questions, PCPs can make a big difference in improved identification and diagnosis of RLS. Keeping the *URGE* mnemonic (*Urge to move, Rest induced, Gets better with activity, and Evening and night accentuation*) in mind can help when one encounters a patient complaining of sleeplessness or excessive daytime sleepiness.²⁴ Also, asking simple questions such as “Do your legs keep you from falling asleep at night?” or “Do your legs bother you or keep you up at night?” can be used to start a dialogue about RLS symptoms.

RLS Psychiatry Perspective

David N. Neubauer, MD



There are several reasons why psychiatrists should be very familiar with RLS. One reason is that people often consult with psychiatrists about their sleep problems, especially when they suffer with insomnia. RLS frequently causes sleep-onset difficulty and occasionally contributes to problems

with sleep maintenance. Psychiatrists should appreciate the role of RLS in the differential diagnosis of insomnia, and they should be in a good position to initiate treatment for RLS or refer patients for further evaluation.

Another reason psychiatrists should have a special interest in RLS is that they already are uniquely familiar with the phenomenology of the subjective experience of RLS patients. The intensely uncomfortable motor restlessness and urge to move is a type of akathisia, similar to that which may occur with antipsychotic medications. Antipsychotic-induced akathisia can be extremely uncomfortable and often has led patients to stop taking their medications. There may be pathophysiological connections between RLS and medication-induced akathisia. One model of RLS etiology is centered on dopamine system dysfunction, which may involve decreased brain iron stores. A key pharmacodynamic action of many antipsychotic medications is postsynaptic dopamine receptor antagonism. This is especially the case with the typical antipsychotics, which are more likely to lead to akathisia. However, RLS clearly differs from antipsychotic-induced akathisia in the usual course of RLS and the characteristic circadian pattern of evening symptoms.

Psychiatrists also need to be familiar with RLS because so many psychotropic medications can exacerbate the symptoms in individuals with vulnerability for primary RLS. Many antidepressants, including the tricyclics and selective serotonin reuptake inhibitors, and antipsychotics will worsen RLS symptoms. Sometimes patients experiencing difficulty falling asleep are prescribed sedating medications, such as quetiapine, that potentially can worsen RLS and sleep-related periodic limb movements, leading to further sleep disruption. An appreciation of which medications are likely to exacerbate RLS is essential for psychiatrists.

In rare cases, patients being treated for RLS with the FDA-approved dopamine agonists may develop new psychiatric symptoms associated with reward system dysfunction. There have been reports of patients developing compulsive behaviors while taking these medications. One example is uncharacteristic gambling. Some patients experience increased sexual urges or other obsessive-compulsive symptoms.

Psychiatrists clearly can play important roles in the identification, evaluation, and treatment of patients with RLS. They should have an understanding of the symptoms, the risks associated with various medications, and the potential side effects of the standard RLS medications. In directing patients toward appropriate management of RLS, psychiatrists have the opportunity to help patients achieve significant symptom relief and quality-of-life improvement.

RLS Neurology Perspective

Christopher J. Earley MB, BCh, PhD, FRCP(I)



I think the primary reason that neurologists should be familiar with RLS is because it is a neurological disorder whose pathology for the moment remains unclear and whose treatment at times can be very challenging. RLS symptoms often coexist with other underlying neurological conditions, such as

peripheral neuropathy, spinal cord lesions, and Parkinson's disease. Sometimes when RLS coexists with an alternative neurological condition, it may be difficult to manage the RLS without simultaneously managing the other neurological issue. Pain-related conditions are probably the most common complicating element that is likely to arise in the efforts to properly manage RLS symptoms. Symptoms of pain that are seen with Parkinson's disease, radiculopathies, peripheral neuropathies, multiple sclerosis, and even in severe arthritic conditions may need to be the primary focus of management efforts before one is able to truly manage the RLS symptoms successfully. Neurologists in general should be prepared to take on the more severe and complex management of this disorder. They should be more familiar with the use of the wide range of medications and their use in combination. As new treatments are advanced, and as we come to a better understanding of the underlying pathophysiology, neurologists should be on the front line of this new and growing knowledge and be prepared to advance new treatments into the clinical practice, particularly for those patients who are inadequately managed with the current lines of treatment.

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1. Concerning the epidemiology of RLS, which of the following is NOT true?

- RLS is often misdiagnosed or undiagnosed
- The prevalence of RLS increases with age
- RLS equally impacts males and females
- Patients with idiopathic RLS are likely to have a family history of RLS

2. Which is NOT one of the 4 diagnostic criteria for RLS?

- Urge to move the legs
- Symptoms worse at rest
- Symptoms worse in the evening or at night
- Symptoms remain unresolved by movement

3. Which of the following statements about RLS is NOT true?

- Dehydration is the largest risk factor for RLS
- Most patients with RLS experience periodic limb movements in sleep (PLMS)
- In pregnancy, RLS symptoms are most common in the third trimester
- Approximately one third of hemodialysis patients have RLS

4. Which of the following RLS treatment considerations is NOT true?

- Multiple types of drugs, including dopamine agonists, benzodiazepines and opiates, are approved by the US Food and Drug Administration for the treatment of moderate to severe RLS
- Medications that may aggravate or trigger RLS symptoms include antidopaminergic medications (antipsychotics and antiemetics), some antidepressants, and antihistamines
- Dopamine agonists have been shown to reduce RLS symptoms and are considered the initial treatment of choice
- Behavioral treatment that increases sensation, such as hot showers or vigorous rubbing of the legs, may provide short-term relief for RLS symptoms

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