Contemporary Challenges and Strategies for Improving Outcomes for Patients With Restless Legs Syndrome

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Abstract

Restless legs syndrome (RLS) is a common neurological disease that is diagnosed solely based on clinical symptoms and may be treated via both nonpharmacologic and pharmacologic means. Despite its somewhat trivial-sounding name, this disease has a very significant impact upon the lives of RLS patients and imposes a substantial burden, as evidenced by direct and indirect costs and loss of productivity. After the introduction of US Food and Drug Administration (FDA)-approved drugs for the management of RLS in 2005, there has been an increase in the awareness of the disease. Increased awareness of RLS has resulted in a greater number of patients receiving treatment for RLS, and in turn, more patients presenting with refractory RLS, in part due to drug-emergent issues such as augmentation. Furthermore, management of the disease is still not optimal. Barriers to obtaining adequate treatment include healthcare providers' lack of knowledge, limited availability of specialists who can provide care to patients presenting with refractory RLS, and access to and cost of medications. Opportunities for managed care to enhance the recognition and treatment of RLS are discussed, with suggestions for improving outcomes in patients with RLS.

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For author information and disclosures, see end of text.

What Is RLS?

Restless legs syndrome (RLS) is a neurological sensory-motor disorder that is characterized by an urge to move the legs when at rest, usually associated with limb discomfort that is very hard for patients to describe.

There are currently 4 essential diagnostic criteria[1]:

1. An urge to move the legs, usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

A fifth criterion was established by the International RLS Study Group in 2012 that includes ruling out mimics of RLS (eg, leg cramps, arthritis, neuropathies, claudication, and positional discomfort) that might confound the diagnosis.

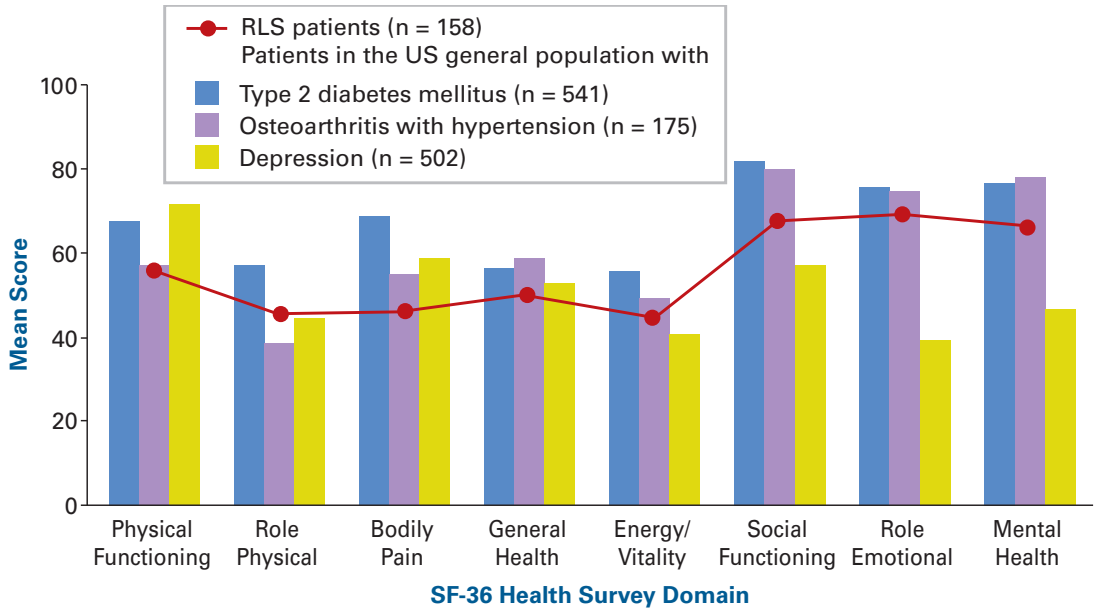
Although not as well known or understood as many of the common conditions (eg, hypertension, diabetes, hyperlipidemia) that primary care physicians (PCPs) see and treat every day, a large epidemiology study[2] (23,052 patients) of primary care practices found that the prevalence of RLS among primary care patients occurring at any frequency (even very infrequently) was 11.1%. This study estimated that about 3% of primary care patients needed treatment, as they had RLS symptoms at least twice a week with an appreciable negative impact on their quality of life.

The current name of RLS has often resulted in the disease being trivialized and not taken seriously by physicians and the public. Therefore the RLS Foundation and professional associations (eg, the International RLS Study Group) have suggested a new name for the disease, Willis-Ekbom Disease (WED), based on the first 2 physicians to describe the disorder.

Burden of RLS

Based on my clinical experience, patients with RLS typically underreport both their symptoms and suffering from the disease. When combined with primary care providers' lack of

■ **Figure 1.** Mean SF-36 Scores of Patients With RLS Compared With Mean SF-36 Scores of Patients With Common Chronic Medical Conditions[4,a]



RLS indicates restless legs syndrome; SF-36, Short Form 36.
[a]RLS patients experienced symptoms at least twice a week during the past 12 months and reported these symptoms to be moderately or extremely distressing.
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knowledge, time, and inclination to delve thoroughly into RLS patients' control of their symptoms, patients often are not fully treated (or are incorrectly treated) and tend to suffer more than patients with comparable but better-known medical conditions.[2]

Direct and Indirect Costs

Several studies have calculated the direct and indirect costs of patients with RLS; however, there have been no studies performed as yet in the United States. Although items such as the cost of drugs, cost of living, insurance expenses, and access to healthcare are different in Europe, where several cost studies have been conducted, the results help shed some light on the economic burden of RLS.

The most recent study examining this issue was conducted in Germany by Dodel et al.[3] The study found that mean direct costs (mostly drugs for RLS and hospitalization for RLS) were 3120 euros per year (approximately US$3900), mean indirect costs (working days lost and productivity loss) were 3260 euros per year (approximately US$4075), and mean income lost due to early retirement was calculated at 1976 euros per year (approximately US$2470). However, these costs were directly proportional to the severity of RLS, with the very severe RLS patients (based on international RLS scores) incurring much higher mean direct costs of 5820 euros (approximately US$7275) per year and indirect costs of 12,676 euros (approximately US$15,845) per year.

Quality of Life

Many studies have demonstrated that RLS patients experience a decrease in quality of life. In a large population study (15,391 subjects questioned with 7.2% reporting symptoms of RLS at any frequency),[4] quality of life was significantly decreased compared with US population norms and was decreased compared with other common chronic disorders (type 2 diabetes, osteoarthritis, and depression) that are associated with significantly decreased quality-of-life scores (Figure 1).

Productivity

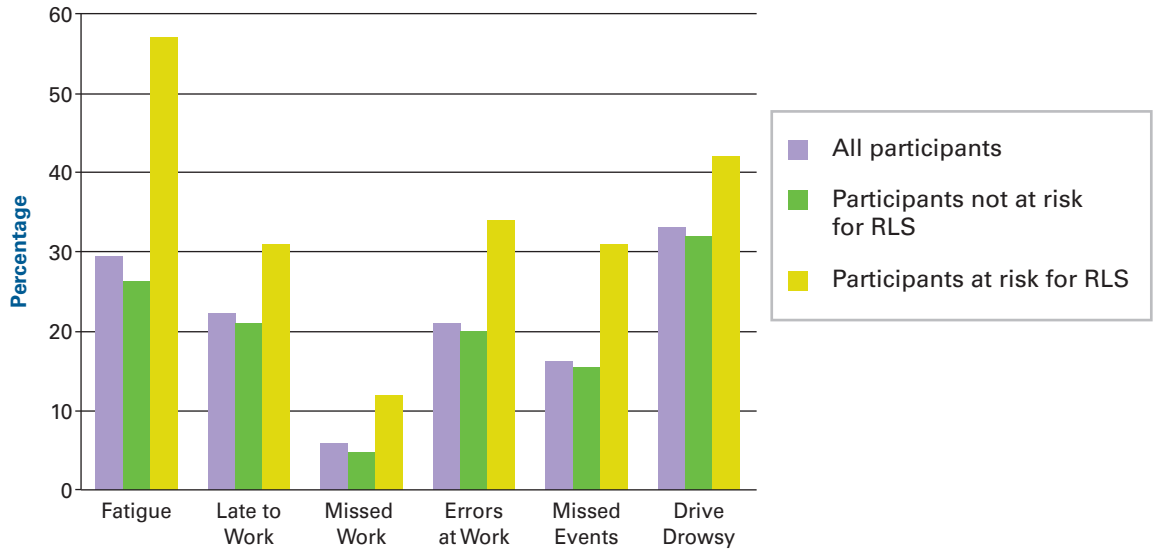
The German study[3] discussed previously found that mean income decrement caused by working days lost and productivity lost due to RLS was 3260 euros (approximately US$4075) per year. In the Sleep in America Poll 2005,[5] errors at work, missed work, and coming late to work were significantly increased for those at risk for RLS (Figure 2).

Challenges in the Diagnosis of RLS

RLS Is Diagnosed Based on Symptoms

As discussed previously, the diagnosis of RLS is based on

Figure 2. Impact of RLS on Daytime Function[5,a]



RLS indicates restless legs syndrome.
[a] $P < .05$ for all symptoms for participants at risk for RLS compared with those not at risk for RLS.
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4 essential criteria. Although many patients can articulate the diagnostic features readily, a large percentage of them have trouble describing their symptoms, which makes it very difficult for physicians to establish the diagnosis. Based on my clinical experience, many patients find their symptoms so strange that they will not mention them to their physicians, or feel that everyone must have them.

Most physicians have very little education about RLS, as medical school curricula typically devote only several minutes to the condition, though a few schools have recently instituted a 1-hour lecture. Public awareness campaigns and increased awareness of RLS after the introduction of 4 FDA-approved RLS drugs have improved diagnostic rates since 2004, when the primary care REST study[2] found that only 13% of patients consulting a physician for their RLS symptoms received a diagnosis of RLS. However, many patients still go undiagnosed for reasons noted above and due to confusion with other diseases that mimic the symptoms of RLS.

Leg cramps are the most common mimic that is confused with RLS. Leg cramps typically occur while at rest in bed at night, cause the person to move, and are relieved by movement. However, leg cramps can be distinguished from RLS by questioning of the patient, which should reveal tightening of a muscle with severe pain that once improved usually does not recur with rest. Neuropathic discomfort (especially the more vague numbness and tingling) may also seem to fulfill the 4 diagnostic criteria (patients notice the symptoms more in the evening when at rest, as they are not distracted); however, when patients further consider this issue, they will report that the symptoms are not improved with activity, nor do they have the almost irresistible urge to move. Arthritis and vascular diseases share some symptoms with RLS but can be easily differentiated from RLS, as they worsen with activity and improve with rest, which is the exact opposite of RLS. People with habitual foot tapping may appear to have RLS, but when queried in more depth will admit that they do not have an urge to move and perform the activity without thinking about it.

There Are No Specific Tests to Diagnose RLS

One of the barriers to establishing a diagnosis of RLS is that there are no laboratory or physical tests that confirm the diagnosis. A sleep study demonstrating numerous periodic limb movements (PLMs) may be suggestive of RLS; however, several other diseases and some drugs are also associated with increased PLM, and the lack of PLM does not rule out RLS. Many RLS patients have a low serum ferritin; however, this may help with treating RLS rather than with diagnosing it. The physical examination typically is normal, and thus the diagnosis must be based solely on the clinical symptoms. In borderline cases, supportive evidence such as the presence of PLM, family history of RLS, and a positive response to treatment with a dopamine agonist may be helpful to verify the diagnosis. RLS occurs more frequently in patients with

conditions such as peripheral neuropathy, diabetes, multiple sclerosis, or hypothyroidism; however, there is no evidence that treating the associated condition improves the RLS.

Although most patients have idiopathic RLS, there is a group of patients with secondary RLS that occurs due to an underlying condition. Laboratory tests are helpful in establishing the cause of RLS in patients with iron deficiency (even without anemia) and for patients with renal failure. Treatment of iron deficiency may result in improvement or full relief of symptoms in patients with iron deficiency, while kidney transplantation may help improve or resolve RLS in dialysis patients.

Challenges in the Treatment of RLS

Available Treatments

Nonpharmacologic Strategies

Nonpharmacologic treatments may be sufficient to treat milder cases of RLS, and may be used as adjunctive therapy for patients with more severe RLS, to possibly reduce their dependence on medications. Interventions include abstaining from alcohol, tobacco, and caffeine, and avoiding medications that worsen RLS (eg, antihistamines, antidepressants, antiemetics). Oral iron supplementation may also be helpful when appropriate. Lifestyle modifications (eg, performing sedentary tasks early in the day, when RLS is less likely to occur), proper sleep hygiene (establishing regular and fixed sleep and wake times, avoiding awake activities while in bed [eg, watching television], not staying in bed while awake for more than 15 minutes), and moderate regular exercise may also be helpful.

Pharmacologic Treatments

Currently, there are only 4 US Food and Drug Administration (FDA)-approved drugs to treat RLS: the 3 dopamine agonist drugs, ropinirole, pramipexole, and rotigotine, and the anticonvulsant drug, gabapentin enacarbil.[6-9] Medications which are not FDA approved but are often used to manage RLS include the anticonvulsant drugs gabapentin and pregabalin, opioids (eg, tramadol, hydrocodone, oxycodone, methadone), and sedative/hypnotics ("sleeping pills"). These drugs are typically necessary for patients with moderate to severe RLS symptoms that cannot be adequately controlled exclusively by nonpharmacologic means. Carbidopa/levodopa has been used off label in the past; however, the use of carbidopa/levodopa has decreased due to its propensity to cause augmentation of RLS symptoms.[10-13]

Augmentation of RLS is defined by a worsening of RLS symptoms (earlier onset, more intense symptoms, spread of symptoms to other body parts, resistance to higher doses of medication) that occurs due to taking a dopamine agonist drug.[14]

Advantages and Disadvantages

Although it has been suggested that dopaminergic dysfunction may be at the root of the etiology of RLS, this has not been proved (which is why it is called idiopathic RLS) and so far can only be inferred from the very positive therapeutic response of RLS symptoms to dopamine drugs. The mechanism of action of the different classes of medications used in the management of RLS symptoms is still unknown. Based on my clinical experience, dopamine agonists are an appropriate choice for very severe symptoms; however, they are associated with augmentation, impulse control disorders, and daytime sedation. The short-acting dopamine agonists are more readily available and less expensive than the long-acting dopamine agonists; however, long-acting dopamine agonists cause less augmentation. Anticonvulsant drugs (eg, gabapentin) are an option for painful RLS symptoms or patients with associated painful comorbid conditions such as neuropathies. They help RLS patients get better-quality sleep (poor sleep quality is common in patients with RLS); however, anticonvulsant drugs may cause daytime sedation. Opioids are an option for refractory RLS cases that have failed or not fully benefited from the use of the dopamine agonists and anticonvulsants. However, opioids should not be prescribed for patients with a history of substance abuse and tolerance, and abuse and dependence are always concerns with opioid therapy. Opioids can also cause constipation, respiratory depression, and sedation.[10-13]

Access to Medications on Managed Care Formularies

While most managed care formularies include the generic short-acting dopamine agonists ropinirole and pramipexole, they may not fully cover extended-release formulations and other approved options (such as the non-dopamine drug, gabapentin enacarbil) for treating RLS. Benefit designs involving higher-tier drug placement, higher copayments, and prior authorization requirements create economic barriers and restrict access to medications, which may result in suboptimal treatment.

Although most patients can be managed initially with the generic short-acting agents, many patients do not respond well to them or after years of treatment may require additional or different therapy due to loss of efficacy, worsening RLS symptoms over time, or drug-emergent problems such as augmentation. Patients who experience insufficient control of symptoms and/or adverse effects with one class of medication should have access to other classes of medication, to help improve outcomes.

In addition, though the supporting literature is scant, my clinical experience with these extended-release drugs has shown that patients who experience RLS symptoms starting in the morning usually benefit from the longer action of these drugs, and it is an option that is important to have available.

Treatment Guidelines

Several treatment algorithms[10-13] for guiding physicians on how to treat RLS have been developed since 2004. Although these guidelines share several basic concepts, they are not fully applicable for clinicians treating RLS in the United States in 2012, as they were created either prior to the availability of 2 of the 4 FDA-approved drugs or in countries where a different set of medications are approved or available for RLS. The lack of an easy-to-follow, up-to-date algorithm impedes many physicians from properly treating RLS patients, particularly those with more severe disease.

Newer algorithms are being worked on and should be published within the next year. An article recently published by the American Academy of Sleep Medicine[15] discusses RLS practice parameters using an evidence-based review of the medical literature and gives both approved and non-approved drug recommendations based upon a complete review of the literature. An International RLS Study Group (IRLSSG) task force has recently published a summary of recommendations for the long-term treatment of RLS[16] on its website (the summary of recommendations should be published in a journal in the near future) that contains an excellent discussion of the pros and cons of all the drugs used for RLS with guidelines for when and how to use them.

Treatment Outcomes

Measures and Rating Scales for RLS

Most of the studies for RLS drugs employ similar outcome measures. The most common one is the International RLS Rating Scale (IRLS),[17] based on 10 questions related to RLS discomfort and impact. The Clinical Global Impression of Improvement scale (CGI-I) is also used very commonly and consists of a 7-point scale that requires the examiner to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. Quality of life is usually measured by the Short Form 36 (SF-36) or the more RLS-specific RLS-Quality of Life questionnaire.[18] Sleep quality is assessed by overnight polysomnography (sleep study), the Medical Outcomes Study Sleep Scale (MOS),[19] or the Pittsburgh Sleep Quality Index.[20]

Improved Outcome Measures

Numerous studies[21-24] have demonstrated symptom improvement (IRLS and CGI-I scales) with all the FDA-approved drugs and many of the non-approved ones[25,26] used to treat RLS. The same is true for sleep quality measures.[21-26] No studies have yet been performed evaluating whether drug intervention may affect productivity.

Improving Outcomes by Improving Symptoms in Patients With RLS

Most RLS patients with less severe symptoms will do very well with any of the approved medications. However, with time, their RLS may become more difficult to manage and require a higher level of expertise to manage. The treatment of patients with comorbidities or severe RLS may also be quite challenging and these patients often are not treated adequately.

Augmentation

Typically, when a patient presents with augmentation, the inclination of the physician is to increase the dose of the dopamine medication, which provides temporary relief (weeks to months usually) but then results in further worsening of augmentation symptoms. Patients may then end up on extremely high doses of these drugs that no longer provide adequate relief.

In my practice, the majority of RLS consultations are currently being referred to me due to augmentation, and this concurs with the experiences of several other national RLS experts, who mentioned in informal discussion that about 75% to 90% of their consultations are referred to them due to augmentation. The scope of this problem is not yet fully known, but a recent study at the tertiary RLS center of Johns Hopkins[27] found that there was a 7% per year rate of augmentation in patients taking pramipexole, and that after 10 years, 70% of those patients had to discontinue their medication.

Based on my clinical experience, the dilemma with treating augmentation is that stopping or reducing the dose of dopamine medication will result in a marked worsening of RLS symptoms that may last several months and most of the time cannot be treated by the current FDA-approved drugs (3 of which are dopamine agonists that may further worsen the symptoms). Treatment often requires a potent opioid. However, most physicians are not aware of this treatment or are not comfortable prescribing potent opioids for RLS. Furthermore, many physicians (even specialists who often

treat difficult RLS cases) are not aware of this augmentation concern or are not that adept at diagnosing it, as the formal diagnostic criteria are somewhat complex.[28] Most patients with severe augmentation do not receive adequate treatment, and typically experience bothersome symptoms unless they can find a specialist with sufficient expertise to treat them.

Severe RLS

Although augmentation is responsible for many patients presenting with severe RLS, other causes such as a natural worsening of the disease over time, tolerance to medication, or exacerbation from RLS-enhancing drugs are also quite common. These patients are often challenging to treat and require individualized therapy to relieve their symptoms. Combination therapy, drug holidays, rotation of 2 or more drugs, or the use of unapproved or unconventional therapy may be necessary to resolve these symptoms, based on my clinical experience. As with augmentation, physicians must have considerable experience and expertise to treat these patients.

Comorbidities and RLS

The coexistence of comorbid conditions and RLS often presents a unique treatment challenge. Drugs that may be necessary to treat serious underlying disorders (eg, depression, psychosis) may markedly worsen RLS, or the comorbid disorder (eg, renal or liver insufficiency, pregnancy, insomnia, increased risk of falling, substance abuse, sleep apnea, obesity) may limit the use of RLS medication. Treating these patients also requires considerable knowledge of RLS and the medications used to treat it. A new useful guide on how to choose drugs in these situations is available from the IRLSSG.[16]

Opportunities for Managed Care

Access to Medications

Managed care can help improve outcomes by ensuring that patients with RLS have access to the full spectrum of available treatments for RLS. Because there are only 4 FDA-approved medications for RLS, access to all of them is often necessary to adequately treat patients. Formularies should include the 2 RLS drugs (gabapentin enacarbil and the rotigotine patch) which do not have generic formulations and the extended-release formulations of the approved dopamine agonists. These drugs are often necessary to treat patients who have failed the older short-acting dopamine agonists (ropinirole and pramipexole). Improved access to medications should help improve patients' quality of life and productivity, and lower the overall cost of care. Administrative barriers often exist that markedly slow the process of the addition of medications to managed care formularies, resulting in limited access to medications; these administrative barriers should be addressed to help improve patient outcomes.

Furthermore, prescribing gabapentin enacarbil as initial treatment could help prevent the issue of treatment-emergent augmentation from occurring in RLS patients. Choosing the rotigotine patch as initial therapy could also potentially reduce problems with augmentation, as rotigotine is also thought to produce fewer augmentation problems than the short-acting dopamine agonists.[29,30] Addressing formulary and cost barriers to medications has the potential to help decrease the number of patients who eventually will need treatment for augmentation.

It is not uncommon for patients to experience inadequate resolution of their symptoms after therapy with all 4 FDA-approved drugs, which creates treatment dilemmas due to the lack of availability of other formulary options, the high out-of-pocket cost of off-formulary drugs, and the lack of familiarity of their use on the part of most physicians. Improved formulary access to drugs with recent peer-reviewed literature supporting their benefit and safety in RLS (eg, pregabalin) should be considered. Further education and training of in-network specialists on appropriate supportive care for patients with RLS along with use of drug therapies as needed and improved patient access to out-of-network RLS experts would also help patients with RLS to receive adequate and appropriate treatment and therefore to achieve sufficient resolution of their symptoms.

Provider Education to Improve Recognition and Treatment

As discussed previously, most practitioners have insufficient knowledge and education about RLS. This frequently results in the under-diagnosis (or even over-diagnosis) of RLS and incorrect treatment of the disease. Based on my clinical experience treating patients with RLS, it is very common to see the correct medication prescribed at an incorrect dose, or ineffective medications or even exacerbating ones prescribed for patients. After the FDA approval of short-acting dopamine agonists in 2005, augmentation is emerging as an increasingly common problem that is not recognized or handled well by PCPs or many specialists.

There are several educational resources for providers currently available. PCPs may benefit from reading the handbook *Clinical Management of Restless Legs Syndrome*[31] (a more current second edition should be available in 2012), while specialists should find the book *Restless Legs Syndrome*[32] to be a helpful reference. However, physician education is best accomplished through meetings (such as Pri-Med) or symposia held with

RLS experts who can share their specialized knowledge about diagnosing and treating RLS with other clinicians.

Access to More Expert Care

Despite the best efforts to educate PCPs and specialists, it will take many years to improve their knowledge base sufficiently so that they can properly manage the many patients with severe RLS, refractory RLS, or severe augmentation. Unfortunately, these patients need help right away but frequently cannot access the care that they need. This is especially true in closed-panel managed care networks that typically do not have a designated RLS expert. Usually this task defaults to an employed or contracted neurologist (often a movement disorder specialist neurologist) or sleep specialist. However, many of these specialists do not have the knowledge and experience to handle these tough-to-treat patients. Therefore, these patients continue to receive inadequate treatment and experience inadequate resolution of their symptoms, or receive therapy that results in significant side effects or exacerbates their RLS symptoms.

Based on my clinical experience treating patients with RLS, it is not uncommon for patients with difficult-to-treat RLS to see 5 to 10 specialists (both inside and outside their managed care system) before consulting with an RLS expert who can help manage RLS symptoms adequately. In my opinion, it would benefit patients with RLS and help improve diagnosis and treatment outcomes if managed care organizations provided patients with access to RLS experts, similar to the access provided for specialized surgical procedures, or to experts in the management of other chronic medical conditions such as systemic lupus erythematosus that may be beyond the expertise of PCPs or network specialists. The lack of sufficient local RLS experts should also be addressed similarly to the lack of local expertise for other medical or surgical conditions that often occurs outside metropolitan areas. It may be difficult to find the nearest RLS expert, but this can be expedited by checking with organizations such as the RLS Foundation and the International RLS Study Group, or by investigating which physicians have published articles on the disease. Experts from the United States, Canada, and Europe are guiding the development of centers of excellence for treating RLS that should make this task much easier.

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