REVIEW

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Restless legs syndrome: Keys to recognition and treatment

ABSTRACT

Restless legs syndrome (RLS) is a common and clinically significant motor disorder increasingly recognized by physicians and the general public, yet still underdiagnosed, underreported, and undertreated. Effective therapies are available, but a high index of suspicion is required to make the diagnosis and start treatment quickly. We now have enough data to support the use of dopaminergic agents, benzodiazepines, antiepileptics, and opioids in these patients.

KEY POINTS

RLS is characterized by paresthesias, usually in the lower extremities. Patients often describe them as "achy" or "crawling" sensations. They develop at rest and are alleviated by movement.

The frequency and severity of RLS symptoms vary from occasional and mild to nightly and severe and preventing sleep.

RLS is most often idiopathic, but it may also be associated with iron deficiency, uremia, pregnancy, folate deficiency, diabetes mellitus, rheumatoid arthritis, fibromyalgia, hypothyroidism, Parkinson disease, and depression.

Treat RLS when quality of life is significantly affected by insomnia or excessive daytime sleepiness.

RESTLESS LEGS SYNDROME (RLS) is not a new diagnosis: it was first described comprehensively 60 years ago.[1] However, it continues to be underdiagnosed, underreported, and undertreated. Effective therapies for this motor disorder are available, but a high index of suspicion is necessary to identify the condition and start treatment in a timely fashion.

Evidence from clinical trials supports the use of dopaminergic agents, benzodiazepines, antiepileptics, and opioids in these patients. The clinician must be familiar with the benefits and risks of these therapies to be able to provide optimal treatment in patients with RLS.

CLINICAL DEFINITION: ACHY, CRAWLING PARESTHESIAS

RLS is a movement disorder characterized by "achy" or "crawling" paresthesias, usually in the lower extremities.[2] These sensations develop at rest and are alleviated by movement. They are much worse in the evening or at night. The severity of the symptoms varies widely; they may occur only occasionally, in a stressful situation, or they may be nightly and severe.[3] RLS is frequently accompanied by disturbances in sleep.[4]

CAUSES ARE UNCLEAR

The pathophysiology of RLS is still unclear. Subcortical central nervous system dysfunction, mainly via the dopaminergic pathway, has been suggested as the mechanism.[5] However, recent radiologic and neuropathologic studies and studies of cerebrospinal fluid have shown that there is iron insufficiency in the brains of patients with RLS,[6–8] with no

neuropathologic changes in the dopaminergic neurons.[6] These findings neither rule out involvement of dopaminergic pathways nor contradict the pharmacologic data, but further implicate the role of iron in RLS.

PREVALENCE

Estimates of the prevalence of RLS in the general population vary greatly and range between 3% and 19%,[9–12] with a significant female predominance.[9,12,13] The symptoms of RLS may begin in childhood or adulthood[14]; however, prevalence increases significantly with age.[9–12] The fact that many of the medical conditions that have been associated with the development of RLS (see below) are more common in the elderly may explain this increased prevalence.

Ethnic background is a major risk factor. Overall, 10% of whites suffer from it, with rates higher (15%) in Northern Europeans and lower (7%) in Mediterranean groups. RLS is unusual (1%) in Asians and rare in blacks.

Heredity

Symptoms of RLS are often incorrectly attributed to anxiety or stress

Up to 92% of patients with RLS have a first-degree relative with the disorder.[4,15,16] In these patients, the family history sometimes suggests an autosomal-dominant mode of inheritance.[16] A family history of RLS is more common in patients with idiopathic RLS than in patients with RLS associated with peripheral neuropathy,[17] and in early-onset RLS (age 45 or earlier) than in late-onset RLS.[4,18] A recent study reported that 83% of twin pairs were concordant for RLS symptoms.[19]

Furthermore, genetic linkage studies have mapped a susceptibility locus to chromosome 12q in one French Canadian family with RLS,[20] and to a locus in chromosome 14q in an Italian family with RLS.[21]

SECONDARY RLS

Most cases of RLS are idiopathic; however, secondary forms of the syndrome are closely associated with other medical disorders or conditions such as iron deficiency,[22,23] uremia,[2,24] pregnancy,[25,26] and polyneuropathy.[27] RLS has also been less often reported in association with folate deficiency,[28] diabetes mellitus,[10,29] rheumatoid arthritis,[30] fibromyalgia,[31] hypothyroidism,[32] Parkinson disease,[33] depression,[11,34] and lower self-reported mental health scores.[11,34] In addition, transient RLS can be induced by spinal anesthesia.[35]

GREATER RECOGNITION NEEDED

Although recognition of RLS is key to useful intervention, many health care providers remain unaware of this condition. RLS is both underreported and underdiagnosed, mainly because patients do not seek medical attention or their symptoms are incorrectly attributed to anxiety or stress. Moreover, few RLS patients who report leg symptoms to a doctor receive a satisfactory explanation.[36] Greater medical recognition of this disorder is needed in view of the availability of medical treatments.

DIAGNOSIS BASED ON HISTORY ALONE

Recommended diagnostic criteria

The diagnosis of RLS is based mainly on the patient history and does not require a sleep study. In May 2002, an RLS diagnosis and epidemiology workshop at the National Institutes of Health, in collaboration with the International RLS Study Group (IRLSSG), determined the following four criteria as essential for a diagnosis of RLS (TABLE 1):

- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
- Unpleasant sensations that begin or worsen during periods of rest or inactivity, such as lying or sitting
- Unpleasant sensations that are partially or totally relieved by movement
- Unpleasant sensations that are worse in the evening or at night than during the day, or that only occur in the evening or at night.[3]

All four of these criteria must be present to make the diagnosis.

Supportive clinical features not essential to the diagnosis of RLS but useful in resolving diagnostic uncertainty include family history, response to treatment with dopaminergic drugs, and periodic limb movements while awake or asleep.[3]

TABLE 1

Criteria for the diagnosis of restless legs syndrome

Essential (patient must have all four)

- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
- Unpleasant sensations begin or worsen during periods of rest or inactivity
- Unpleasant sensations are partially or totally relieved by movement
- Unpleasant sensations are worse in the evening

Supportive

- Positive family history
- Response to treatment with dopaminergics
- Presence of periodic limb movements

How patients describe the sensations

Because the uncomfortable and unpleasant sensations that manifest with RLS are not the same as usual sensory experiences, people often have difficulty describing them.[3] Frequent descriptors include need to move, crawling, tingling, restlessness, ache, cramp, pain, electric sensation, tension, itching, and worms moving.[3,15] Most patients describe the sensation as deep-seated,[15] typically bilateral and felt primarily in the lower legs, but often in the thighs and sometimes in the feet.

Exacerbating factors, other features

Factors other than immobility that may exacerbate the condition include cold, heat, fatigue, and stress.[15] Arms are eventually involved in 14% to 50% of cases.[4,15,16,37] The spread to the arms tends to correlate with a longer duration of symptoms and severity; RLS rarely occurs without leg involvement.[3,37] RLS may also involve other body parts, such as the hips, trunk, and even the face.[3,38]

Sleep complaints

Sleep complaints in RLS patients are very common, and they focus more on the inability to fall asleep or to return to sleep than on the number of awakenings or the amount of movement while asleep.[4]

Periodic limb movements in sleep are present in most RLS patients and can be associated with a poor quality of sleep and repeated nocturnal awakenings.[16] These movements are characterized by periodic episodes of repetitive limb movements caused by contractions of the muscles that occur during sleep; they tend to be grouped into series, with a reasonably periodic pattern of one movement usually occurring every 20 to 40 seconds.[3] Studies have reported a prevalence of periodic limb movements during sleep as high as 80% in RLS patients who underwent a sleep study (all-night polysomnography),[16] with an additional 7.8% of patients being diagnosed on a second test.[16]

The polysomnographic recording of periodic limb movements during sleep may also help confirm the diagnosis of RLS, and in fact these movements are often present before the person falls asleep. Since these "awake" movements are not scored by polysomnographic technologists, the interpreting sleep physician must pay careful attention in order to detect them.[39] Interestingly, only 17% of patients with periodic limb movements during sleep experience RLS. However, periodic limb movements during sleep with RLS may produce insomnia or hypersomnia or both. A trial of dopaminergic therapy with suppression of periodic limb movements during sleep may be required to determine whether these movements are truly responsible for the patient's sleep symptoms.

Patients describe RLS sensations as crawling, tingling, itching, worms moving

DIFFERENTIAL DIAGNOSIS

Other entities that can present with motor restlessness in the lower extremities and that need to be excluded include akathisia, noctur-

nal leg cramps, vesper's curse, and anxiety states.

Akathisia

Akathisia refers to a feeling of inner restlessness. In typical cases, the seated patient may stroke the scalp, cross and uncross the legs, rock the trunk, squirm in the chair, get out of the chair often to pace back and forth, and even make noises such as moaning.[40] Akathisia is often a side effect of drugs that block dopamine receptors, such as the antipsychotics.[40]

Although akathisia and RLS share some clinical features, the symptoms are more much likely to be exacerbated by night and repose in RLS than in akathisia, and akathisia is more rarely accompanied by periodic limb movements during sleep.[41]

Nocturnal leg cramps

Nocturnal leg cramps may be idiopathic or associated with structural disorders, leg positioning, or electrolyte disturbances. They are characterized by localized muscular pain that is easily differentiated from RLS dysesthesias.

First evaluate for iron deficiency or other treatable conditions that cause or worsen RLS

Vesper's curse

Vesper's curse—lumbosacral and associated leg pain and paresthesias arousing patients from a sound sleep—occurs in patients with congestive heart failure in association with lumbar spinal stenosis.[42] An increase in right atrial filling pressure reflected in elevated paraspinal venous volumes within the reduced confines of a stenotic lumbar spine is believed to be the precipitating cause of this syndrome.

Other conditions to rule out

Other possibilities to consider in the differential diagnosis include "sleep starts" (sudden jerking contractions of the extremities that occur at sleep onset), myoclonus of different origin, and venous vascular problems. In fact, RLS is often misdiagnosed as a venous vascular problem.

THE INITIAL WORKUP

The first step in the management of RLS is to evaluate the patient for conditions that can produce or exacerbate this syndrome. Some of these conditions are treatable (eg, iron deficiency). The clinician should also be knowledgeable about drugs associated with the development of RLS.

The initial workup of these patients should include a comprehensive evaluation for the following conditions:

- Iron deficiency
- End-stage renal disease
- Pregnancy
- Neuropathy
- Drug side effects.

Iron deficiency

A high incidence of iron deficiency has been noted among patients with RLS,[1] and iron deficiency (with or without anemia) has been shown to be an important contributor to the development of RLS.[23] Different studies have shown that there is less iron in the brain of RLS patients than in the brain of age-matched healthy controls.[6,8]

In a study involving neuropathologic examination of brains from patients with RLS, iron staining and H-ferritin staining were markedly decreased in the substantia nigra of RLS patients.[6] This local iron insufficiency in the substantia nigra could impair dopaminergic function by limiting tyrosine hydroxylase activity or the expression of dopamine transporters and receptors.[6]

An extension of this autopsy study involving quantitative analysis of proteins responsible for iron homeostasis in the neuromelanin cells of the substantia nigra revealed a profile that is consistent with iron insufficiency.[43]

Ferritin levels lower than 50 ng/L (normal range 18.0–300 in men, 18.0–150 in women) correlate significantly with a greater severity of RLS and decreased sleep efficiency.[22] Some studies have described groups of patients with RLS and iron deficiency that responded favorably to iron therapy.[23,44] Improvement was greatest for those with the lowest initial serum ferritin level (≤ 45 ng/L).[23] In contrast, a randomized double-blind, placebo-controlled trial of oral iron sulfate for the treatment of RLS failed to demonstrate any improvement in self-reported symptoms of RLS, in sleep quality, or in quality of life.[45] Nonetheless, the mean ferritin level in the patients treated with iron in this study was 134.8 ng/mL.[45]

Although these data are inconclusive, recent studies have underscored the role of iron as a major factor in the pathophysiology of RLS, providing a rationale for raising low ferritin levels by iron supplementation.

We routinely check serum ferritin levels and percent iron saturation as part of the initial medical evaluation for RLS. A trial of oral iron therapy is warranted if the ferritin levels are low (≤ 50 ng/L),[46] even though this cut-off is well within normal limits.

End-stage renal disease

The prevalence of RLS in patients with end-stage renal disease ranges from 20% to 62%[2,24] is often severe, and may be among the most troublesome components of the uremic syndrome. Moreover, a small study showed that the severity of periodic limb movement disorder (RLS was not investigated) was a better predictor of death in end-stage renal disease than serum albumin, urea reduction ratio, or hematocrit.[47]

These results underscore the importance of RLS in this patient population. The severity of RLS in patients with end-stage renal disease has been associated with the inability to maintain the immobility necessary to complete dialysis sessions.[2] Premature discontinuation of hemodialysis could have significant consequences in the electrolyte and volume status of these patients. Hemodialysis does not cure this problem, but patients can expect a substantial improvement of RLS symptoms after successful kidney transplantation.[48] Dopaminergics, anticonvulsants, benzodiazepines, and opioids can be used to treat RLS in uremic patients.

More recently, and quite to the contrary, lung transplantation patients have been shown to have a high incidence of RLS. A prospective evaluation study of the effects of lung transplantation on RLS is in progress.[49]

RLS in pregnancy is usually not severe, tends to resolve after delivery

Pregnancy

Pregnant women have a higher prevalence of RLS (19% to 23%), especially during the third trimester of pregnancy.[25,26] Nonetheless, few of these patients have severe symptoms, and the symptoms resolve after delivery in most cases.[25,26]

Folate supplementation. Reduced serum folate levels have been associated with RLS in pregnant women,[25] and a small study suggested that folate supplementation might decrease the incidence of RLS in this population.[28]

Reassuring the patient. In a different study, most pregnant women with RLS who told their general practitioner about their symptoms were not provided with a satisfactory explanation.[26] Reassuring patients that they have a common condition that will almost certainly disappear after delivery should help alleviate their concerns.

Prenatal considerations. However, RLS during pregnancy may be a marker for recurrence of chronic symptoms after initial remission. We encourage an adequate dietary intake of iron-rich foods, folate supplementation, and measurement of ferritin and folate levels. We try to avoid drug therapy as much as possible.

Neuropathy

RLS has been associated with peripheral neuropathy,[27] but this association remains controversial. Neuropathy in patients with RLS may be difficult to identify by history alone due to the clinical homogeneity between idiopathic and neuropathic RLS, and to the high rate of subclinical neuropathy in RLS patients.[15,17] Nerve conduction velocities and electromyographic studies may be useful, especially if the sensory symptoms of RLS are atypical. Moreover, these tests can detect subtle peripheral neuropathy, and lead to the evaluation for treatable causes of neuropathy.[5]

A study revealed that people with diabetes were four times more likely to have RLS than nondiabetic patients.[10] However, some of those patients might have diabetic small-fiber neuropathy, with features that can mimic RLS with predominantly nocturnal dysesthesias.[10] Gabapentin is the drug of choice in RLS patients who have a neuropathic component.

Drug-induced RLS

A variety of drugs have been said to either cause or worsen RLS. Different neuroleptics have been associated with the development of RLS.[50,51] Antidepressant-induced RLS has been mostly reported with selective serotonin reuptake inhibitors (SSRI) including sertra-

TABLE 2

Some drugs used in the treatment of idiopathic restless legs syndrome

NAME	DOSE
Carbidopa-levodopa	Start at 25 mg/100 mg (1/2 to 1 tablet) 30-60 minutes before bedtime
Clonazepam	Start at 0.25 mg at bedtime, increase slowly to 2 mg at bedtime
Gabapentin	Start at 300 mg at bedtime, with incremental increases of 300 mg at bedtime, up to 1,200 mg at bedtime
Pergolide	Start at 0.05 mg at bedtime, increase dose by 0.05 mg every few days, dose may be increased up to 0.5 mg at bedtime
Pramipexole	Start at 0.125 mg at bedtime, dose may be increased up to 0.75 mg at bedtime
Ropinirole	Start at 0.25 mg at bedtime, increase slowly to 1 mg at bedtime

line,[52] paroxetine,[53] and fluoxetine.[54] Nonetheless, RLS can also be induced by other antidepressants such as mirtazapine,[55] mianserin,[56] and tricyclic antidepressants.

A study showed that regular use or overuse of non-opioid analgesics—frequently combined with caffeine—is associated with an increased risk of RLS in patients on long-term antidepressant therapy.[57] Finally, RLS can also develop during opiate withdrawal,[58] and with the use of antiepileptics such as zonisamide[59] or lithium.[60] RLS has been also associated with other commonly used drugs, such as ethanol, histamine-2 blockers, and beta-blockers.

Treat RLS only if patient insomnia or daytime sleepiness is significant

DECIDE WHETHER AND HOW TO TREAT

Once we have ruled out secondary causes of RLS, we have to decide if we are going to start treatment for idiopathic RLS. Treatment should be considered when quality of life is significantly affected by insomnia or excessive daytime sleepiness. The next step is to select an appropriate treatment, either nonpharmacologic or pharmacologic.

NONPHARMACOLOGIC THERAPIES

Nondrug therapies are an option for patients with mild symptoms of RLS once the symptoms reach the point at which they cause sleep deprivation.

Options include relaxation therapy, stress reduction, biofeedback, and acupuncture.[61] Abstinence from caffeine, nicotine, and alcohol can also be recommended. Before treating, the clinician should examine the patient's lifestyle and look for opportunities for lifestyle modifications, especially regarding sleep habits.

It is worth noting that none of these therapies has been proven effective in clinical trials. With this in mind, reassurance might be the only necessary intervention when symptoms are intermittent and the syndrome is not accompanied by disturbances in sleep. However, the patient should be informed about the availability of drug therapies, which include dopamine precursors (levodopa), dopamine agonists (ergot and non-ergot), opioids, benzodiazepines, and antiepileptics (gabapentin) (TABLE 2). Others, such as clonidine, propranolol, and amantadine, may also be effective. We will discuss specific drugs in the following sections.

DOPAMINE PRECURSORS

Levodopa

Several controlled and open trials have established that levodopa is effective in idiopathic and uremic RLS.[62–64] Furthermore, a long-term study showed that it tends to remain effective for at least 2 years, with stability of the dosage regimen, and without serious side

effects in most patients.[65]

Levodopa is used in conjunction with a dopa-decarboxylase inhibitor such as carbidopa or benserazide to decrease levodopa dosage requirements and levodopa-induced adverse effects such as nausea, headache, dry mouth, and gastrointestinal symptoms.[62]

Carbidopa-levodopa rebound and augmentation

Although carbidopa-levodopa was traditionally considered the drug of choice for the treatment of RLS, the development of "rebound" or "augmentation" limits its therapeutic usefulness.[66,67] Rebound is the end-of-dose development of RLS symptoms in the morning hours after awakening.[66] Augmentation is a shift of daily onset of symptoms to 2 hours or more earlier than the period of daily onset before treatment.[3] Augmentation can also be diagnosed if therapy results in two or more of these features:

- Increased intensity of symptoms temporally related to an increase in the medication dosage
- Decreased intensity of symptoms temporally related to a decrease in the medication dosage
- Shorter latency period until the onset of symptoms at rest
- Involvement of previously unaffected limbs or body parts
- Shorter duration of treatment effect, with or without the appearance or worsening of periodic limb movements while awake.[3]

Augmentation is more common and more clinically significant than rebound,[3] and is greater for patients with more severe RLS symptoms and for patients on higher doses of levodopa.[67] Augmentation is more common with levodopa than with any other dopaminergic agent because it has the shortest half-life of any other drug in its class. The development of augmentation usually indicates that the drug needs to be stopped, or that another drug, usually a dopamine agonist, should be tried.

DOPAMINE AGONISTS

Dopamine agonists act directly on dopamine receptors and have been used successfully in RLS. They seem to pose less risk of augmentation[3]; however, these data are not based on randomized, controlled trials comparing levodopa and dopamine agonists. Dopamine agonists are divided into ergot derivatives and non-ergot derivatives.

Ergot-based dopamine receptor agonists

Pergolide, a potent, long-acting dopamine agonist with a half-life of 7 to 16 hours, has proved to be an effective alternative in the treatment of RLS.[68,69] Studies have shown that the use of pergolide in RLS improves symptoms, duration of symptoms throughout the day, sleep efficiency, and periodic limb movements per hour during sleep.[68,69] Furthermore, an open follow-up of one of these studies found that the beneficial effects of pergolide on RLS symptoms and sleep disturbances persist for at least 1 year.[70]

Nausea is commonly seen but is well controlled with antiemetics in most patients,[70] and may be avoided with a very slow titration upward. Domperidone is the antiemetic of choice, because other antiemetics may block dopamine receptor activity and thereby exacerbate RLS.

Other less common side effects include nasal congestion, constipation, pruritus, headache, dizziness, and abdominal pain.[70] Because pergolide is an ergoline, it has the potential of causing pleural, pericardial, and retroperitoneal fibrosis, but these are rare.[71,72] Valvular heart disease has also been associated with the use of pergolide.[73]

As an alternative, ergot-based dopamine agonists have shown benefit

Cabergoline is another long-acting dopamine agonist (half-life > 65 hours) that has been shown to be effective and well tolerated in RLS, especially in patients with severe RLS and patients who developed augmentation under levodopa therapy.[74] Cabergoline might be useful in patients who have symptoms throughout the day, since they can be treated with a single dose.

Non-ergot-based dopamine receptor agonists

Newer dopamine agonists not derived from ergot, such as pramipexole and ropinirole, have also been proved to be effective for the treatment of RLS and are said to have fewer side effects than the other current treatments.[75–78]

Pramipexole. In a recent double-blind crossover study, 10 RLS patients received either placebo or pramipexole for 1 month, and then crossed over to the other treatment for another month. Pramipexole dramatically reduced the index of periodic limb movements during sleep to normal values and alleviated leg discomfort at bedtime and during the night.[75] In some patients the use of pramipexole was associated with side effects such as nausea, constipation, loss of appetite, dizziness, and daytime fatigue[75]; however, these side effects were mild and usually disappeared within 1 week after starting treatment or increasing the dosage.[75] At follow-up, these patients revealed no evidence of a decrease in the therapeutic effect of pramipexole after a mean of 7.8 months of treatment.[79]

Ropinirole. A randomized, double-blind, placebo-controlled, crossover study[77] showed significant improvement of symptoms in RLS patients with the use of ropinirole. More recently, a prospective, double-blind, randomized study of 284 RLS patients from 10 European countries showed that ropinirole improves RLS compared with placebo, with benefits apparent by 1 week.[78] It has recently been approved by the US Food and Drug Administration (FDA) for use in RLS. In fact, it is the only drug currently indicated for RLS. After initial titration to minimize nausea, very small doses are required relative to those used for Parkinson disease: 1.0 mg in the evening, 1 hour before the usual onset of symptoms is adequate for maintenance therapy.

OPIOIDS

Open-label and double-blind studies on the effect of opioids on RLS have shown an improvement in leg paresthesias, motor restlessness, daytime alertness, sleep-related arousals, sleep efficiency, and periodic limb movements during sleep.[80,81] However, two double-blind, placebo-controlled trials comparing carbidopa-levodopa against propoxyphene showed that dopaminergics were far more effective than opioids for reducing leg movements before and during sleep.[82,83]

Opioid use carries a risk for abuse and addiction, although this is uncommon.[84] In patients with augmentation, problems with tolerance, or addiction, methadone 5 to 20 mg per day can be effective.

Other reported adverse effects include daytime fatigue, migraine headaches, hangover and grogginess, paradoxical hyperalerting response, and constipation.[84] Development or worsening of sleep apnea in patients on long-term opioid therapy has also been reported.[84]

BENZODIAZEPINES

Benzodiazepines, in particular clonazepam, are used for the treatment of idiopathic and uremic RLS.[85,86] However, the American Academy of Sleep Medicine recommends these drugs mainly for patients with periodic limb movement disorder, and possibly for RLS.[87] These drugs do not diminish periodic limb movements on polysomnography, but they do minimize the resulting arousals.

Extra caution is needed when using benzodiazepines in the elderly. This age group is particularly sensitive to undesirable side effects such as profound confusion, cognitive impairment, and falls. Other risks with benzodiazepines include tolerance and daytime sleepiness. Taking the dose earlier in the evening or switching to a shorter-acting benzodiazepine such as temazepam can reduce daytime sleepiness.

Drugs for RLS are usually to be taken in the evening or at bedtime

ANTICONVULSANTS

Gabapentin is an anticonvulsant that is effective and well tolerated in the treatment of RLS. An open-label study and a randomized placebo-controlled trial of the effect of gabapentin on RLS revealed subjective symptom improvement and a reduction of periodic limb movements during sleep as detected with polysomnography.[88,89] The patients whose symptoms included pain benefited most from gabapentin in one of these trials.[89] Gabapentin is also an effective treatment for RLS in hemodialysis patients[90] and patients with associated neuropathy.

OTHER DRUGS

Carbamazepine,[91] clonidine,[92] propanolol,[93] and amantadine[94] have shown various degrees

of effectiveness for the treatment of RLS. However, most of this information comes from a few small studies, most of which were open-label trials or case series. Further randomized controlled trials are required to validate the use of these drugs for the treatment of RLS.

TREATMENT RECOMMENDATIONS

Practice parameters for the treatment of RLS published in 2004 by the American Academy of Sleep Medicine favor dopaminergic agents, in particular levodopa and the dopaminergic agonists pergolide, pramipexole, and ropinirole.[95] Ropinirole is the only drug currently approved by the FDA for RLS. For now, it appears to be the drug of first choice in patients whose RLS requires treatment.

In our practice, we start iron supplementation if the patient qualifies (ferritin ≤50 μg/L). If the ferritin is above this cut-off, we prefer to start with one of the non-ergot-derivative dopamine agonists. We reserve levodopa for patients with mild intermittent symptoms, ie, whom we treat only when needed.

Dosing

In contrast to the treatment of Parkinson disease, repeated dosing during the day beginning in the morning is usually not needed in RLS. However, in some patients earlier dosing during the day might be required during the course of treatment.

In addition, it is extremely important to remember that the doses of the drugs used in the treatment of RLS are usually much lower than for Parkinson disease.

We use gabapentin in patients who have a neuropathic component to their presentation. We prefer to avoid the use of benzodiazepines in the elderly, and in general we avoid opioids due to their lower level of effectiveness and their potential for addiction. There is usually no crossover between medications: if one medication in a drug class does not work, another agent from that same class might. In general, drugs are usually taken in the evening or at bedtime.

REFERENCES

1. **Ekbom KA.** Restless legs syndrome. Acta Med Scand 1945; 158(suppl):1–123.
2. **Winkelman JW, Chertow GM, Lazarus JM.** Restless legs syndrome in end-stage renal disease. Am J Kidney Dis 1996; 28:372–378.
3. **Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J.** Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003; 4:101–119.
4. **Winkelmann J, Wetter TC, Collado-Seidel V, et al.** Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 2000; 23:597–602.
5. **Tan EK, Ondo W.** Restless legs syndrome: clinical features and treatment. Am J Med Sci 2000; 319:397–403.
6. **Connor JR, Boyer PJ, Menzies SL, et al.** Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003; 61:304–309.
7. **Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ.** MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001; 56:263–265.
8. **Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP.** Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000; 54:1698–1700.
9. **Ohayon MM, Roth T.** Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res 2002; 53:547–554.
10. **Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C.** Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000; 160:2137–2141.
11. **Ulfberg J, Nystrom B, Carter N, Edling C.** Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord 2001; 16:1159–1163.
12. **Egan D, O'Dubhghaill C, McNamee S, Mulkerrin E, O'Keefe ST.** A community study of the prevalence of restless legs. Ir Med J 2003; 96:153.
13. **Ulfberg J, Nystrom B, Carter N, Edling C.** Restless legs syndrome among working-aged women. Eur Neurol 2001; 46:17–19.
14. **Walters AS, Picchietti D, Hening W, Lazzarini A.** Variable expressivity in familial restless legs syndrome. Arch Neurol 1990; 47:1219–1220.
15. **Ondo W, Jankovic J.** Restless legs syndrome: clinicoetiologic correlates. Neurology 1996; 47:1435–1441.
16. **Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P.** Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997; 12:61–65.
17. **Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC.** Subclinical sensory neuropathy in late-onset restless legs syndrome. Neurology 2000; 55:1115–1121.
18. **Allen RP, Earley CJ.** Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med 2000; 1:11–19.
19. **Ondo WG, Vuong KD, Wang Q.** Restless legs syndrome in monozygotic twins: clinical correlates. Neurology 2000; 55:1404–1406.
20. **Desautels A, Turecki G, Montplaisir J, Sequeira A, Verner A, Rouleau GA.** Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. Am J Hum Genet 2001; 69:1266–1270.
21. **Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G.** Autosomal dominant restless legs syndrome maps on chromosome 14q. Brain 2003; 126:1485–1492.
22. **Sun ER, Chen CA, Ho G, Earley CJ, Allen RP.** Iron and the restless legs syndrome. Sleep 1998; 21:371–377.
23. **O'Keeffe ST, Gavin K, Lavan JN.** Iron status and restless legs syndrome in the elderly. Age Ageing 1994; 23:200–203.
24. **Hui DS, Wong TY, Ko FW, et al.** Prevalence of sleep disturbances in chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 2000; 36:783–788.
25. **Lee KA, Zaffke ME, Baratte-Beebe K.** Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Womens Health Gend Based Med 2001; 10:335–341.

26. **Goodman JD, Brodie C, Ayida GA.** Restless leg syndrome in pregnancy [letter]. BMJ 1988; 297:1101–1102.
27. **Rutkove SB, Matheson JK, Logigian EL.** Restless legs syndrome in patients with polyneuropathy. Muscle Nerve 1996; 19:670–672.
28. **Botez MI, Lambert B.** Folate deficiency and restless-legs syndrome in pregnancy. N Engl J Med 1977; 297:670.
29. **Banerji NK, Hurwitz LJ.** Restless legs syndrome, with particular reference to its occurrence after gastric surgery. Br Med J 1970; 4:774–775.
30. **Reynolds G, Blake DR, Pall HS, Williams A.** Restless leg syndrome and rheumatoid arthritis. Br Med J (Clin Res Ed) 1986; 292:659–660.
31. **Yunus MB, Aldag JC.** Restless legs syndrome and leg cramps in fibromyalgia syndrome: a controlled study. BMJ 1996; 312:1339.
32. **O'Keefe ST.** Restless legs syndrome. Arch Intern Med 1996; 156:243–248.
33. **Krishnan PR, Bhatia M, Behari M.** Restless legs syndrome in Parkinson's disease: a case-controlled study. Mov Disord 2003; 18:181–185.
34. **Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K.** Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 2000; 54:1064–1068.
35. **Hogl B, Frauscher B, Seppi K, Ulmer H, Poewe W.** Transient restless legs syndrome after spinal anesthesia: a prospective study. Neurology 2002; 59:1705–1707.
36. **O'Keeffe ST, Noel J, Lavan JN.** Restless legs syndrome in the elderly. Postgrad Med J 1993; 69:701–703.
37. **Michaud M, Chabli A, Lavigne G, Montplaisir J.** Arm restlessness in patients with restless legs syndrome. Mov Disord 2000; 15:289–293.
38. **Valentino RM, Lim L, Foldvary-Schaefer N.** Periodic limb movements during nocturnal wakefulness in restless legs syndrome [abstract]. Sleep 2005; 28:A265.
39. **Fukunishi I, Kitaoka T, Shirai T, Kino K.** Facial paresthesias resembling restless legs syndrome in a patient on hemodialysis [letter]. Nephron 1998; 79:485.
40. **Fahn S.** Hypokinesia and hyperkinesia. In: Goetz CG. Textbook of Clinical Neurology. 2nd ed. Philadelphia: Elsevier Science (USA); 2003:279–297.
41. **Walters AS, Hening W, Rubinstein M, Chokroverty S.** A clinical and polysomnographic comparison of neuroleptic-induced akathisia and the idiopathic restless legs syndrome. Sleep 1991; 14:339–345.
42. **LaBan MM, Viola SL, Femminineo AF, Taylor RS.** Restless legs syndrome associated with diminished cardiopulmonary compliance and lumbar spinal stenosis—a motor concomitant of "Vesper's curse." Arch Phys Med Rehabil 1990; 71:384–388.
43. **Connor JR, Wang XS, Patton SM, et al.** Decreased transferrin receptor expression by neuromelanin cells in restless legs syndrome. Neurology 2004; 62:1563–1567.
44. **Nordlander NB.** Therapy in restless legs. Acta Med Scand 1953; 145:453–457.
45. **Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR.** A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. Eur Neurol 2000; 43:70–75.
46. **National Heart, Lung, and Blood Institute Working Group on Restless Legs Syndrome.** Restless legs syndrome: detection and management in primary care. Am Fam Phys 2000; 62:108–114.
47. **Benz RL, Pressman MR, Hovick ET, Peterson DD.** Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis 2000; 35:1052–1060.
48. **Winkelmann J, Stautner A, Samtleben W, Trenkwalder C.** Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. Mov Disord 2002; 17:1072–1076.
49. **Yataco J, Masri FA, Golish JA.** Prevalence of restless legs syndrome in lung transplantation patients. Chest. In press.
50. **Wetter TC, Brunner J, Bronisch T.** Restless legs syndrome probably induced by risperidone treatment. Pharmacopsychiatry 2002; 35:109–111.
51. **Kraus T, Schuld A, Pollmacher T.** Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine. J Clin Psychopharmacol 1999; 19:478–479.
52. **Hargrave R, Beckley DJ.** Restless leg syndrome exacerbated by sertraline. Psychosomatics 1998; 39:177–178.
53. **Sanz-Fuentenebro FJ, Huidobro A, Tejadas-Rivas A.** Restless legs syndrome and paroxetine. Acta Psychiatr Scand 1996; 94:482–484.
54. **Bakshi R.** Fluoxetine and restless legs syndrome. J Neurol Sci 1996; 142:151–152.
55. **Bahk WM, Pae CU, Chae JH, Jun TY, Kim KS.** Mirtazapine may have the propensity for developing a restless legs syndrome? A case report. Psychiatry Clin Neurosci 2002; 56:209–210.
56. **Paik IH, Lee C, Choi BM, Chae YL, Kim CE.** Mianserin-induced restless legs syndrome. Br J Psychiatry 1989; 155:415–417.
57. **Leutgeb U, Martus P.** Regular intake of non-opioid analgesics is associated with an increased risk of restless legs syndrome in patients maintained on antidepressants. Eur J Med Res 2002; 7:368–378.
58. **Scherbaum N, Stuper B, Bonnet U, Gastpar M.** Transient restless legs-like syndrome as a complication of opiate withdrawal. Pharmacopsychiatry 2003; 36:70–72.
59. **Chen JT, Garcia PA, Alldredge BK.** Zonisamide-induced restless legs syndrome. Neurology 2003; 60:147.
60. **Terao T, Terao M, Yoshimura R, Abe K.** Restless legs syndrome induced by lithium. Biol Psychiatry 1991; 30:1167–1170.
61. **Jinsheng H.** Acupuncture treatment of restless leg syndrome. J Tradit Chin Med 2001; 21:312–316.
62. **Trenkwalder C, Stiasny K, Pollmacher T, et al.** L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. Sleep 1995; 18:681–688.
63. **Von Scheele C.** Levodopa in restless legs. Lancet 1986; 2:426–427.
64. **Saletu M, Anderer P, Hogl B, et al.** Acute double-blind, placebo-controlled sleep laboratory and clinical follow-up studies with a combination treatment of rr-L-dopa and sr-L-dopa in restless legs syndrome. J Neural Transm 2003; 110:611–626.
65. **Von Scheele C, Kempi V.** Long-term effect of dopaminergic drugs in restless legs. A 2-year follow-up. Arch Neurol 1990; 47:1223–1224.
66. **Guilleminault C, Cetel M, Philil P.** Dopaminergic treatment of restless legs and rebound phenomenon. Neurology 1993; 43:445.
67. **Allen RP, Earley CJ.** Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996; 19:205–213.
68. **Wetter TC, Stiasny K, Winkelmann J, et al.** A randomized controlled study of pergolide in patients with restless legs syndrome. Neurology 1999; 52:944–950.
69. **Earley CJ, Yaffee JB, Allen RP.** Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. Neurology 1998; 51:1599–1602.
70. **Stiasny K, Wetter TC, Winkelmann J, et al.** Long-term effects of pergolide in the treatment of restless legs syndrome. Neurology 2001; 56:1399–1402.
71. **Pfitzenmeyer P, Foucher P, Dennewald G, et al.** Pleuropulmonary changes induced by ergoline drugs. Eur Respir J 1996; 9:1013–1019.
72. **Shaunak S, Wilkins A, Pilling JB, Dick DJ.** Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. J Neurol Neurosurg Psychiatry 1999; 66:79–81.
73. **Pritchett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE.** Valvular heart disease in patients taking pergolide. Mayo Clin Proc 2002; 77:1280–1286.
74. **Stiasny K, Robbecke J, Schuler P, Oertel WH.** Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline—an open clinical trial. Sleep 2000; 23:349–354.
75. **Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B.** Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology 1999; 52:938–943.
76. **Saletu M, Anderer P, Saletu-Zyhlarz G, Hauer C, Saletu B.** Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. Eur Arch Psychiatry Clin Neurosci 2002; 252:185–194.
77. **Adler CH, Hauser R, Sethi K, Caviness JN, Marlor L, Hentz JG.** Ropinirole is beneficial for restless legs syndrome: a placebo-controlled crossover trial [abstract]. Neurology 2003; 60(suppl 1):A439.
78. **Trenkwalder C, Garcia-Borreguero D, Montagna P, et al.** Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12-week, randomized, placebo controlled study in 10

European countries. J Neurol Neurosurg Psychiatry 2004; 75:92–97.
79. **Montplaisir J, Denesle R, Petit D.** Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol 2000; 7(suppl 1):27–31.
80. **Hening WA, Walters A, Kavey N, Gidro-Frank S, Cote L, Fahn S.** Dyskinesias while awake and periodic movements in sleep in restless legs syndrome: treatment with opioids. Neurology 1986; 36:1363–1366.
81. **Walters AS, Wagner ML, Hening WA, et al.** Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep 1993; 16:327–332.
82. **Allen RP, Kaplan PW, Buchholz DW, Earley CJ, Walters JK.** Double-blinded, placebo controlled comparison of high dose propoxyphene and moderate dose carbidopa/levodopa for treatment of periodic limb movements in sleep. Sleep Res 1992; 21:166.
83. **Kaplan P, Allen R, Buchholz D, Walters J.** A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep 1993; 16:717–723.
84. **Walters AS, Winkelmann J, Trenkwalder C, et al.** Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord 2001; 16:1105–1109.
85. **Read DJ, Feest TG, Nassim MA.** Clonazepam: effective treatment for restless legs syndrome in uraemia. Br Med J (Clin Res Ed) 1981; 283:885–886.
86. **Montagna P, Sassoli de Bianchi L, Zucconi M, Cirignotta F, Lugaresi E.** Clonazepam and vibration in restless legs syndrome. Acta Neurol Scand 1984; 69:428–430.
87. **Chesson AL Jr, Wise M, Davila D, et al.** Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 1999; 22:961–968.
88. **Happe S, Klosch G, Saletu B, Zeitlhofer J.** Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology 2001; 57:1717–1719.
89. **Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G.** Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002; 59:1573–1579.
90. **Thorp ML, Morris CD, Bagby SP.** A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. Am J Kidney Dis 2001; 38:104–108.
91. **Telstad W, Sorensen O, Larsen S, Lillevold PE, Stensrud P, Nyberg-Hansen R.** Treatment of the restless legs syndrome with carbamazepine: a double blind study. Br Med J (Clin Res Ed) 1984; 288:444–446.
92. **Wagner ML, Walters AS, Coleman RG, Hening WA, Grasing K, Chokroverty S.** Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. Sleep 1996; 19:52–58.
93. **Derom E, Elinck W, Buylaert W, van der Straeten M.** Which beta-blocker for the restless leg? Lancet 1984; 1:857.
94. **Evidente VG, Adler CH, Caviness JN, Hentz JG, Gwinn-Hardy K.** Amantadine is beneficial in restless legs syndrome. Mov Disord 2000; 15:324–327.
95. **Littner MR, Kushida C, McDowell Anderson W, et al.** Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 2004; 27:557–600.

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