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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.

**R**ESTLESS LEGS SYNDROME (RLS) is not a new diagnosis: it was first described comprehensively 60 years ago.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> RLS is frequently accompanied by disturbances in sleep.<sup>4</sup>

## 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.<sup>5</sup> 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,<sup>6–8</sup> with no

neuropathologic changes in the dopaminergic neurons.<sup>6</sup> 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%,<sup>9-12</sup> with a significant female predominance.<sup>9,12,13</sup> The symptoms of RLS may begin in childhood or adulthood<sup>14</sup>; however, prevalence increases significantly with age.<sup>9-12</sup> 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

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

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

### ■ 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,<sup>22,23</sup> uremia,<sup>2,24</sup> pregnancy,<sup>25,26</sup> and polyneuropathy.<sup>27</sup> RLS has also been less often reported in association

with folate deficiency,<sup>28</sup> diabetes mellitus,<sup>10,29</sup> rheumatoid arthritis,<sup>30</sup> fibromyalgia,<sup>31</sup> hypothyroidism,<sup>32</sup> Parkinson disease,<sup>33</sup> depression,<sup>11,34</sup> and lower self-reported mental health scores.<sup>11,34</sup> In addition, transient RLS can be induced by spinal anesthesia.<sup>35</sup>

### ■ 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.<sup>36</sup> 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.<sup>3</sup>
- 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.<sup>3</sup>

**Symptoms of RLS are often incorrectly attributed to anxiety or stress**

**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.<sup>3</sup> Frequent descriptors include need to move, crawling, tingling, restlessness, ache, cramp, pain, electric sensation, tension, itching, and worms moving.<sup>3,15</sup> Most patients describe the sensation as deep-seated,<sup>15</sup> 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.<sup>15</sup> Arms are eventually involved in 14% to 50% of cases.<sup>4,15,16,37</sup> The spread to the arms tends to correlate with a longer duration of symptoms and severity; RLS rarely occurs without leg involvement.<sup>3,37</sup> RLS may also involve other body parts, such as the hips, trunk, and even the face.<sup>3,38</sup>

### 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.<sup>4</sup>

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.<sup>16</sup> 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.<sup>3</sup> 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),<sup>16</sup> with an additional 7.8% of patients being diagnosed on a second test.<sup>16</sup>

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.<sup>39</sup> 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.

### ■ DIFFERENTIAL DIAGNOSIS

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

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

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.<sup>40</sup> Akathisia is often a side effect of drugs that block dopamine receptors, such as the antipsychotics.<sup>40</sup>

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.<sup>41</sup>

### 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.

### 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.<sup>42</sup> 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,<sup>1</sup> and iron deficiency (with or without anemia) has been shown to be an important contributor to the development of RLS.<sup>23</sup> Different studies have shown that there is less iron in the brain of RLS patients than in the brain of age-matched healthy controls.<sup>6,8</sup>

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.<sup>6</sup> 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.<sup>6</sup>

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.<sup>43</sup>

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.<sup>22</sup> Some studies have described groups of patients with RLS and iron deficiency that responded favorably to iron therapy.<sup>23,44</sup> Improvement was greatest for those with the lowest initial serum ferritin level ( $\leq 45$  ng/L).<sup>23</sup> 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.<sup>45</sup> Nonetheless, the mean ferritin level in the patients treated with iron in this study was 134.8 ng/mL.<sup>45</sup>

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

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 ( $\leq 50$  ng/L),<sup>46</sup> 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%.<sup>2,24</sup> 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.<sup>47</sup>

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.<sup>2</sup> 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.<sup>48</sup> 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.<sup>49</sup>

### Pregnancy

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

**Folate supplementation.** Reduced serum

folate levels have been associated with RLS in pregnant women,<sup>25</sup> and a small study suggested that folate supplementation might decrease the incidence of RLS in this population.<sup>28</sup>

**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.<sup>26</sup> 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,<sup>27</sup> 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.<sup>15,17</sup> 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.<sup>5</sup>

A study revealed that people with diabetes were four times more likely to have RLS than nondiabetic patients.<sup>10</sup> However, some of those patients might have diabetic small-fiber neuropathy, with features that can mimic RLS with predominantly nocturnal dysesthesias.<sup>10</sup> 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.<sup>50,51</sup> Antidepressant-induced RLS has been mostly reported with selective serotonin reuptake inhibitors (SSRI) including sertra-

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

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,<sup>52</sup> paroxetine,<sup>53</sup> and fluoxetine.<sup>54</sup> Nonetheless, RLS can also be induced by other antidepressants such as mirtazapine,<sup>55</sup> mianserin,<sup>56</sup> 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.<sup>57</sup> Finally, RLS can also develop during opiate withdrawal,<sup>58</sup> and with the use of antiepileptics such as zonisamide<sup>59</sup> or lithium.<sup>60</sup> RLS has been also associated with other commonly used drugs, such as ethanol, histamine-2 blockers, and beta-blockers.

#### ■ 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.<sup>61</sup> 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.<sup>62–64</sup> 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

**Treat RLS only if patient insomnia or daytime sleepiness is significant**



effects in most patients.<sup>65</sup>

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.<sup>62</sup>

### **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.<sup>66,67</sup> Rebound is the end-of-dose development of RLS symptoms in the morning hours after awakening.<sup>66</sup> Augmentation is a shift of daily onset of symptoms to 2 hours or more earlier than the period of daily onset before treatment.<sup>3</sup> 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.<sup>3</sup>

Augmentation is more common and more clinically significant than rebound,<sup>3</sup> and is greater for patients with more severe RLS symptoms and for patients on higher doses of levodopa.<sup>67</sup> 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 augmenta-

tion<sup>3</sup>; 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.<sup>68,69</sup> 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.<sup>68,69</sup> 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.<sup>70</sup>

Nausea is commonly seen but is well controlled with antiemetics in most patients,<sup>70</sup> 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.<sup>70</sup> Because pergolide is an ergoline, it has the potential of causing pleural, pericardial, and retroperitoneal fibrosis, but these are rare.<sup>71,72</sup> Valvular heart disease has also been associated with the use of pergolide.<sup>73</sup>

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.<sup>74</sup> 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.<sup>75–78</sup>

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



**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.<sup>75</sup> In some patients the use of pramipexole was associated with side effects such as nausea, constipation, loss of appetite, dizziness, and daytime fatigue<sup>75</sup>; however, these side effects were mild and usually disappeared within 1 week after starting treatment or increasing the dosage.<sup>75</sup> 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.<sup>79</sup>

**Ropinirole.** A randomized, double-blind, placebo-controlled, crossover study<sup>77</sup> 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.<sup>78</sup> 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.<sup>80,81</sup> 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.<sup>82,83</sup>

Opioid use carries a risk for abuse and addiction, although this is uncommon.<sup>84</sup> 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, hang-over and grogginess, paradoxical hyperalerting response, and constipation.<sup>84</sup> Development or worsening of sleep apnea in patients on long-term opioid therapy has also been reported.<sup>84</sup>

### ■ BENZODIAZEPINES

Benzodiazepines, in particular clonazepam, are used for the treatment of idiopathic and uremic RLS.<sup>85,86</sup> However, the American Academy of Sleep Medicine recommends these drugs mainly for patients with periodic limb movement disorder, and possibly for RLS.<sup>87</sup> 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.

### ■ 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.<sup>88,89</sup> The patients whose symptoms included pain benefited most from gabapentin in one of these trials.<sup>89</sup> Gabapentin is also an effective treatment for RLS in hemodialysis patients<sup>90</sup> and patients with associated neuropathy.

### ■ OTHER DRUGS

Carbamazepine,<sup>91</sup> clonidine,<sup>92</sup> propranolol,<sup>93</sup> and amantadine<sup>94</sup> have shown various degrees

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



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.<sup>95</sup> 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  $\leq 50$   $\mu\text{g/L}$ ). 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. 

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