The Management of Restless Legs Syndrome: An Updated Algorithm

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Abstract

Restless legs syndrome (RLS) is a common disorder. The population prevalence is 1.5% to 2.7% in a subgroup of patients having more severe RLS with symptoms occurring 2 or more times a week and causing at least moderate distress. It is important for primary care physicians to be familiar with the disorder and its management. Much has changed in the management of RLS since our previous revised algorithm was published in 2013. This updated algorithm was written by members of the Scientific and Medical Advisory Board of the RLS Foundation based on scientific evidence and expert opinion. A literature search was performed using PubMed identifying all articles on RLS from 2012 to 2020. The management of RLS is considered under the following headings: General Considerations; Intermittent RLS; Chronic Persistent RLS; Refractory RLS; Special Circumstances; and Alternative, Investigative, and Potential Future Therapies. Nonpharmacologic approaches, including mental alerting activities, avoidance of substances or medications that may exacerbate RLS, and oral and intravenous iron supplementation, are outlined. The choice of an alpha$_2$-delta ligand as first-line therapy for chronic persistent RLS with dopamine agonists as a second-line option is explained. We discuss the available drugs, the factors determining which to use, and their adverse effects. We define refractory RLS and describe management approaches, including combination therapy and the use of high-potency opioids. Treatment of RLS in pregnancy and childhood is discussed.

Restless legs syndrome (RLS) is characterized by an urge to move the legs, usually in association with limb discomfort.[1] The symptoms occur at rest, are relieved by movement, and are worse in the evening and at night. They should not be solely accounted for by other conditions, such as arthritis, leg cramps, positional discomfort, or myalgia.[2] RLS is usually associated with involuntary, rhythmic brief contractions of the legs during sleep (and at times during relaxed wakefulness) known as periodic limb movements. The severity and frequency of symptoms vary widely. For symptoms occurring at least twice a week and resulting in moderate or severe distress, the prevalence is 1.5% to 2.7%.[3,4] For many patients, RLS is a cause of disabling sleep-onset or maintenance insomnia and may result in reduced quality of life,[5] depression, and increased risk of suicide.[6,7] RLS is familial in about 50% of patients[8] but may be related to acquired conditions, especially iron deficiency, pregnancy, and chronic renal failure. Several predisposing candidate genes have been identified through genome-wide association studies.[9] Evidence suggests that RLS is associated with low intracerebral iron stores due to as yet unclear defects in iron homeostatic mechanisms and downregulation of striatal dopamine receptors.[10,11] Increased cerebral glutamate and decreased adenosine may also play a role in the pathophysiologic mechanism of the disorder.[12] Dopamine agonists, alpha$_2$-delta calcium channel ligands,

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ARTICLE HIGHLIGHTS

- Iron status should be assessed in all patients with restless legs syndrome (RLS) and appropriate oral or intravenous iron therapy considered.

- Unless contraindicated, alpha$_2$-delta ligands are first-line agents for treatment of chronic persistent RLS, with dopamine agonists second-line drugs.

- Low-dose opioid therapy is indicated for the management of refractory RLS with appropriate precautions.

and opioids are effective therapies, but understanding of the mechanisms through which they work will depend on better elucidation of the underlying disease pathogenesis.

The high prevalence of RLS requires that primary care physicians familiarize themselves with the condition and take a leading role in its management. The Medical Advisory Board of the nonprofit RLS Foundation constructed an algorithm for the management of RLS in 2004 that was revised in 2013, with both papers published in *Mayo Clinic Proceedings*.[13,14] In the past 8 years, advances have been made in the management of the disorder, including the following developments: the long-term risks of chronic dopaminergic therapy, especially augmentation, have been better understood; large controlled trials of pregabalin[15] and oxycodone[16] have been published; in the setting of the overuse of prescription opioids for the management of chronic pain, consensus recommendations on their responsible use for refractory restless legs have been developed[17]; the use of intravenous iron and its methods of administration have been better delineated through controlled trials[18]; more attention has been paid to RLS management in pregnancy, lactation, and childhood; and active research is exploring other novel RLS therapies. As a result of these developments, the RLS Foundation Scientific and Medical Advisory Board decided the time was right for the issuing of an updated algorithm of treatment for RLS.

Many rigorous evidence-based reviews of the treatment of RLS have been published, including several since publication of the 2013 revised algorithm. These include updates from the American Academy of Neurology[19] and the International Parkinson and Movement Disorder Society[20] and a guideline paper on first-line treatments and management of dopaminergic augmentation jointly produced by the International RLS Study Group, the European RLS Study Group, and the RLS Foundation.[21] Although evidence-based reviews are valuable, they may not in isolation be helpful for the primary care physician trying to determine the optimal therapy for a particular patient. Conclusions from such reviews are constrained by the breadth and quality of the published peer-reviewed literature. The highest level of evidence usually requires large multicenter studies that are almost always funded by the manufacturer of the drug to be tested. Thus, the degree of evidence to support a specific medication may depend on whether a pharmaceutical manufacturer has been willing to fund large studies. For similar reasons, very few large comparative studies of different drugs have been published. Whereas large controlled trials are essential, they usually test short-term use of drugs. Long-term studies generally provide lower levels of evidence, being either uncontrolled prospective or retrospective studies. Nevertheless, such data on continued use of medication in the community are highly relevant for medical practice for a disease that is often lifelong. For many of these reasons, evidence-based reviews of specific disorders generally make authoritative statements on the degree of evidence for each medication. They are, however, not always conducive to the development of practical algorithms for the management of disorders of varying severity and a lengthy natural history. For relatively rare conditions that are managed predominantly by specialists with considerable experience and a reasonable knowledge of the published literature, evidence-based reviews may be adequate. However, for primary

care physicians seeking a practical approach to common disorders, evidence-based reviews alone may be insufficient.

To prepare the updated algorithm, the RLS Foundation Scientific and Medical Advisory Board established a task force from among its members who produced and revised a draft that was submitted for approval to the other members of the board. The authors have had many years of experience in the treatment of RLS and have conducted original research on this disorder. Some have been members of task forces that have produced the previously discussed evidence-based reviews. The effort was supported by the Board of Directors and Executive Director of the RLS Foundation, but this article is entirely the work of the physicians and scientists on the Scientific and Medical Advisory Board. It is based on both a detailed knowledge of the literature, including evidence-based assessments, and expert opinion from practical experience. A literature search was performed using PubMed identifying all articles on RLS from 2012 (the year before the publication of the previous algorithm) to 2020. Relevant studies of RLS management were included in our recommendations. We recognize that a different group of specialists might have produced a somewhat different algorithm, but we believe that our approach reflects current thinking about the management of RLS. We expect that the development of new medications and further research on existing ones may alter clinical approaches in the future. Of note, the US Food and Drug Administration (FDA) has approved pramipexole, ropinirole, rotigotine patch, and gabapentin enacarbil for the treatment of RLS, and thus all other drugs discussed are being used "off label." Although we have attempted to produce an accurate document, it is the responsibility of individual physicians to familiarize themselves with all aspects of the medications they prescribe and to decide whether a specific drug is appropriate for a particular patient.

Box 1. Road Map to the Algorithm

General Considerations
- Assess systemic iron status and consider appropriate iron replacement if needed, especially in patients with refractory restless legs syndrome (RLS).
- Consider and manage any coexisting sleep disorders.
- Consider the role of medications in causing or exacerbating RLS.

Intermittent RLS
- Use nonpharmacologic strategies, including mental alerting and a trial of abstinence from caffeine and alcohol.
- Consider intermittent use of carbidopa/levodopa, low-potency opioids, or benzodiazepine agonists.

Chronic Persistent RLS
- Use alpha$_2$-delta calcium channel ligands, unless contraindications exist.
- Use a nonergot dopamine agonist if alpha$_2$-delta calcium channel ligands are contraindicated or ineffective.
- If dopamine agonists are being used, monitor for augmentation and impulse control disorders and modify treatment accordingly.

Refractory RLS
- Consider combination therapy with alpha$_2$-delta calcium channel ligands, dopamine agonists, or benzodiazepines.
- Consider opioid monotherapy.

Box 1 presents a "road map" to the algorithm; each section is discussed in more detail in the following sections.

GENERAL CONSIDERATIONS

Iron Therapy

There is substantial clinical research demonstrating that patients with RLS have lower than normal iron stores in some regions of the brain and that iron therapy can be beneficial, even if the patient is not anemic or does not have a systemic iron deficiency (Box 2).[10,18,22,23] However, because there is currently no accepted method to assess a patient's brain iron stores, clinicians should evaluate iron status in all patients with RLS, even in the absence of typical factors associated with iron deficiency, such as menorrhagia, gastrointestinal blood loss, or frequent blood donations. A full iron assessment should include serum iron, ferritin, total iron-binding capacity, and percentage transferrin saturation and should be measured in the early morning after an overnight fast.

On the basis of a consensus of RLS experts,[18] it is recommended that all RLS

Box 2. Iron Therapy

- Determine the patient's iron status (early morning, fasting iron panel: serum ferritin, iron, total iron-binding capacity, and percentage transferrin saturation).[18]
- If serum ferritin concentration is ≤75 μg/L and transferrin saturation is <45%, administer an oral iron preparation (elemental iron 65 mg) with 100 to 200 mg of vitamin C every 1 or 2 days on an empty stomach. (Note that in the presence of inflammation or malignant disease, serum ferritin concentration may be misleadingly high, and thus transferrin saturation <20% may be a more accurate measure of iron deficiency.)
- Consider intravenous administration of iron if transferrin saturation is <45% and (1) serum ferritin concentration is <100 μg/L and a more rapid response is desired than is possible with oral iron; (2) oral iron cannot be adequately absorbed because of disorders of the gastrointestinal system, bariatric surgery, or chronic inflammatory conditions; (3) oral iron is not tolerated; and (4) restless legs symptoms do not improve despite an adequate (3-month) trial of oral intake of iron.

patients with serum ferritin concentration of 75 μg/L (to convert to pmol/L, multiply by 2.247) or less and transferrin saturation below 45% should receive a trial of oral iron therapy. Serum measures of systemic iron status, however, do not consistently predict those who will respond to iron treatment. If serum ferritin concentration is below the lower limit of normal based on the patient's sex and age, a cause for iron deficiency should also be pursued. Of note, serum ferritin is an acute phase reactive protein and may take up to 6 weeks after recovery from an inflammatory or infective event before returning to normal. In the presence of acute or chronic inflammation or malignant disease, serum ferritin concentration can be misleadingly high. In those situations, transferrin saturation below 20% may be a more accurate measure of systemic iron deficiency.

A common oral iron regimen is 325 mg of ferrous sulfate (65 mg elemental iron) in combination with 100 to 200 mg of vitamin C with each dose to enhance absorption once daily or once every second day. More frequent administration of iron may reduce absorption. There are data from nonhuman primate studies that iron is taken up by the brain from the blood at higher rates at night than in the morning.[24] Because the treatment object is to increase specifically brain iron concentrations, the use of oral iron at night may be more advantageous.

Iron tablets should ideally be taken on an empty stomach to enhance absorption, but if gastrointestinal symptoms develop, they can be taken with food (not with substances high in calcium). Iron should not be prescribed empirically because it may result in iron overload, especially in patients with previously unsuspected hemochromatosis. Follow-up ferritin determinations are needed, initially after 3 to 4 months and then every 3 to 6 months until the serum ferritin level is greater than 100 μg/L.[18] If there is not an ongoing cause for iron deficiency, oral iron therapy can be stopped, but treatment should recommence if RLS worsens unless serum ferritin concentration is 300 μg/L or higher, the usually accepted safe upper limit.

Intravenous administration of iron should be first-line iron therapy if moderate to severe chronic persistent or refractory RLS is present (see later for definitions) and either serum ferritin concentration is between 76 μg/L and 100 μg/L or a more rapid response is desired than is possible with oral iron. (Intravenous administration of iron is recommended as first-line iron therapy if serum ferritin concentration is between 76μg/L and 100 μg/L because absorption of oral iron at these higher ferritin levels is likely to be minimal.) Intravenous iron therapy is also recommended if oral iron cannot be adequately absorbed because of disorders of the gastrointestinal system or bariatric surgery, oral iron is not tolerated, and RLS symptoms do not improve despite an adequate (3-month) trial of oral intake of iron. According to a consensus of RLS experts,[18] the base requirement for any use of intravenous iron therapy in RLS is that the serum ferritin concentration should be less than 100 μg/L (and not affected by inflammation) and transferrin saturation less than 45%.

All of the intravenous iron formulations that are currently FDA approved for treatment of iron deficiency anemia may be of value in treatment of RLS. The majority of the class I clinical trials for intravenous iron therapy in RLS used, however, ferric carboxymaltose.[25-27] This has been shown

to be effective at doses of 1000 mg administered as a single dose of 1000 mg or as 2 doses of 500 mg at 5- to 7-day intervals, but the clinical response to treatment is rarely immediate and may be delayed for 4 to 6 weeks or longer. The percentage of patients responding ranges between 37% and 59%. Intravenous ferric carboxymaltose causes hypophosphatemia in up to 39% of patients.[28] The clinical significance of this finding is uncertain, but repeated use may possibly contribute to osteopenia. Other intravenous iron preparations that can be considered are low-molecular-weight iron dextran (1000 mg) and ferumoxytol (1020 mg), both as single infusions. Although low-molecular-weight iron dextran has a lower risk of life-threatening allergic reactions (estimated at 1 per 300,000 uses) compared with the older high-molecular-weight iron dextran, a test dose (25 mg) should be given first. Pretreatment with diphenhydramine is unnecessary and may exacerbate restless legs. Use of any other iron formulations for RLS should follow the clinical guidelines recommended for treatment of iron deficiency anemia. If there has been an adequate response to an intravenous iron infusion but symptoms recur, repeated infusions can be given in at least 12-week intervals as long as serum ferritin concentration is below 300 μg/L and transferrin saturation is less than 45%. In patients with a questionable response, a second infusion can be considered, especially if the serum ferritin concentration is still less than 100 μg/L.

Role of Medications in Causing or Worsening RLS

Clinical experience and open-label studies suggest that administration of most antidepressants may be associated with initiation or worsening of RLS (Box 3).[29] An exception is bupropion,[30] which should be considered for management of depression in RLS patients. However, if other antidepressants are deemed necessary to treat a mood disturbance, they should be introduced and the effects on RLS monitored. The mechanisms by which antidepressants and antihistamines

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Box 3. Role of medications in causing or worsening RLS

Consider whether antidepressants, neuroleptic agents, dopamine-blocking antiemetics such as metoclopramide, or sedating antihistamines (including those found in nonprescription medications) may be contributing and whether discontinuation is possible without causing the patient harm.

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might worsen RLS are uncertain. Dopamine-blocking agents presumably act by exacerbating the effect of downregulation of dopamine receptors characteristic of RLS.

Assessment for Other Sleep Disorders
See Box 4.

INTERMITTENT RLS
Intermittent RLS is defined as restless legs symptoms that are troublesome enough to require treatment but occur on average less than twice per week (Figure 1).

Nonpharmacologic Strategy
Nonpharmacologic therapies may obviate the need for medications in mild cases of RLS and may allow a reduction in dosage in patients with moderate or severe disease (Box 5). Mental alerting activities and abstinence from caffeine and alcohol are based on empirical observations, and the mechanisms by which they may be effective are uncertain.

Medication
Intermittent use of the medications listed in Box 6 may be helpful. Carbidopa/levodopa, 25 mg/100 mg ($\frac{1}{2}$ -1 tablet), can be used for RLS that occurs intermittently in the evening, at bedtime, or on waking during the night or for RLS associated with specific activities, such as airplane or lengthy car rides or theater attendance. Controlled-release

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Box 4. Assessment for Other Sleep Disorders

Concurrent sleep disorders, sleep fragmentation, or insufficient sleep may exacerbate RLS. Clinicians should especially inquire about symptoms of obstructive sleep apnea and pursue appropriate testing as indicated; in some cases, sleep apnea treatment results in improvements in RLS, eliminating the need for medications. Patients with RLS may have other causes of insomnia, including depression, anxiety, or behavioral (eg, excessive caffeine intake), and these may need independent treatment.

FIGURE 1. Approach to the management of intermittent restless legs syndrome (RLS).
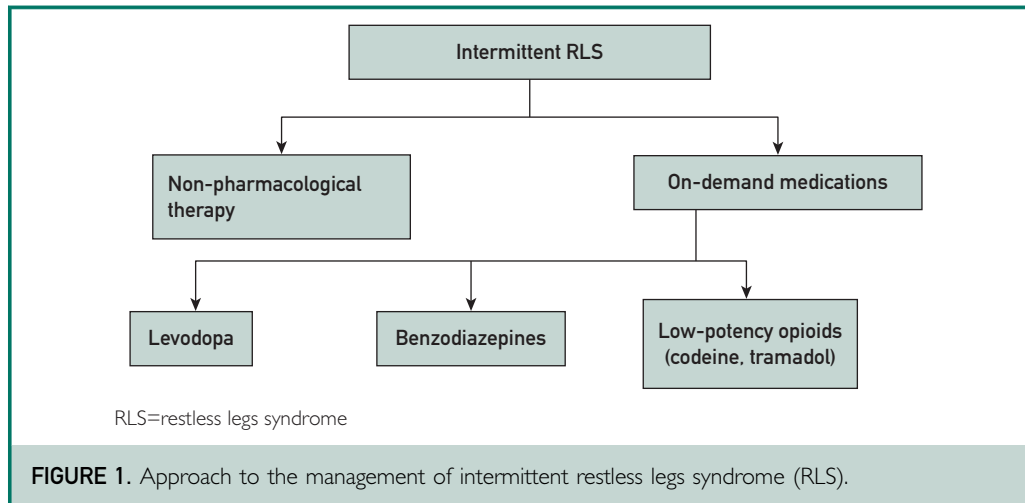
carbidopa/levodopa, 25 mg/100 mg (1 tablet), can be used alternatively before bed for RLS that awakens the patient during the night. Even the controlled-release form has a relatively short duration of action and may not produce sustained efficacy if RLS persists throughout much of the night. Controlled trials have shown efficacy of both preparations.[31] For maximal absorption, levodopa should not be taken with high-protein foods.

Problems with levodopa treatment include augmentation and rebound. Augmentation (drug-induced worsening of RLS, which is discussed in more detail later) may occur in up to 70% of patients taking levodopa daily, and the risk increases with daily doses of 200 mg or more.[32] As a result, levodopa should be prescribed only for intermittent use, such as 3 or fewer times a week, although a lower risk of augmentation with

such use has not been firmly established. Rebound, the recurrence of RLS in the early morning, occurs in 20% to 35% of patients taking levodopa.[33] (Because the action of dopamine agonists generally commences 90 to 120 minutes after ingestion, these agents are less helpful once symptoms have started and are rarely prescribed for intermittent RLS.)

Intermittent use of low-potency opioids usually before bed can be effective. Doses of 30 to 90 mg of codeine, in combined preparations with acetaminophen, or 50 to 100 mg of tramadol can be taken before bed or during the night. Constipation or nausea may occur. Tramadol can rarely induce seizures and is the only nondopaminergic drug associated occasionally with the development of augmentation.

Intermittent use of benzodiazepines or benzodiazepine receptor agonists before sleep may be considered, especially if the patient has another cause of poor sleep in addition to RLS, such as insomnia associated with psychophysiologic factors. Short-acting agents, such as zolpidem (5-10 mg) or zaleplon (5-10 mg), may be helpful for sleep-onset insomnia caused by RLS; intermediate-acting agents, such as temazepam (15-30 mg) or eszopiclone (1-3 mg), may be helpful for RLS that awakens the patient later in the night. Lower doses should be used in women and in older patients. Adverse effects include risk of falls during

Box 5. Non-pharmacological Strategy

- Determine the patient's iron status and replace iron as indicated (see General Considerations).
- Recommend mental alerting activities, such as video games or crossword puzzles, to reduce symptoms at times of boredom.
- Consider a trial of abstinence from caffeine and alcohol.
- Consider the possibility of other co-occurring sleep disorders, most importantly obstructive sleep apnea.
- Consider the role of medications in causing or exacerbating restless legs (see General Considerations).

Box 6. Medications for Intermittent RLS

Intermittent use of the following medications may be helpful:
- Carbidopa/levodopa, 25 mg/100 mg, or controlled release, 25 mg/100 mg
- Low-potency opioids, such as codeine or tramadol
- Benzodiazepines or benzodiazepine agonists, such as temazepam, zolpidem, zaleplon, or eszopiclone

the night and cognitive difficulties, especially in the elderly. The fast-onset, short-acting agents, especially zolpidem, may cause sleepwalking and sleep-related eating disorder, with RLS patients especially predisposed to these effects.[34,35] Long-acting agents, such as clonazepam, may result in more adverse effects, such as unsteadiness during the night and drowsiness or cognitive impairment in the morning, and should generally be avoided unless used for comorbid psychiatric conditions with careful monitoring for adverse effects. There are no adequate controlled trials of benzodiazepines for RLS,[31] and it is likely that the drugs act by treating the associated insomnia or concurrent anxiety rather than the sensory or motor symptoms of the disorder.

CHRONIC PERSISTENT RLS

Chronic persistent RLS is defined as restless legs symptoms that are frequent and troublesome enough to require daily treatment, usually occurring on average at least twice a week and resulting in moderate or severe distress (Figure 2).

Nonpharmacologic Strategy

The nonpharmacologic approach for chronic persistent RLS is the same as for intermittent RLS. Iron stores should be checked in all patients.

Medication

Dopamine agonists are an effective treatment option for RLS and were formerly used for first-line treatment of RLS. However, because of increasing awareness of the high incidence of dopamine agonist−induced worsening of RLS symptoms known as augmentation and the risk for development of impulse control disorders, alpha$_2$-delta ligands should, when not contraindicated, be tried first (Box 7). Regular follow-up of RLS patients receiving medications long term is important. The frequency depends on the response to treatment; initially, this should be at least every 3 months, with stable patients reassessed at least every year.

Gabapentin and pregabalin (Table 1) are usually administered as once- or twice-daily doses in the late afternoon or evening or before sleep. It is recommended to start treatment 1 to 2 hours before usual onset

FIGURE 2. Approach to the management of chronic persistent restless legs syndrome (RLS).
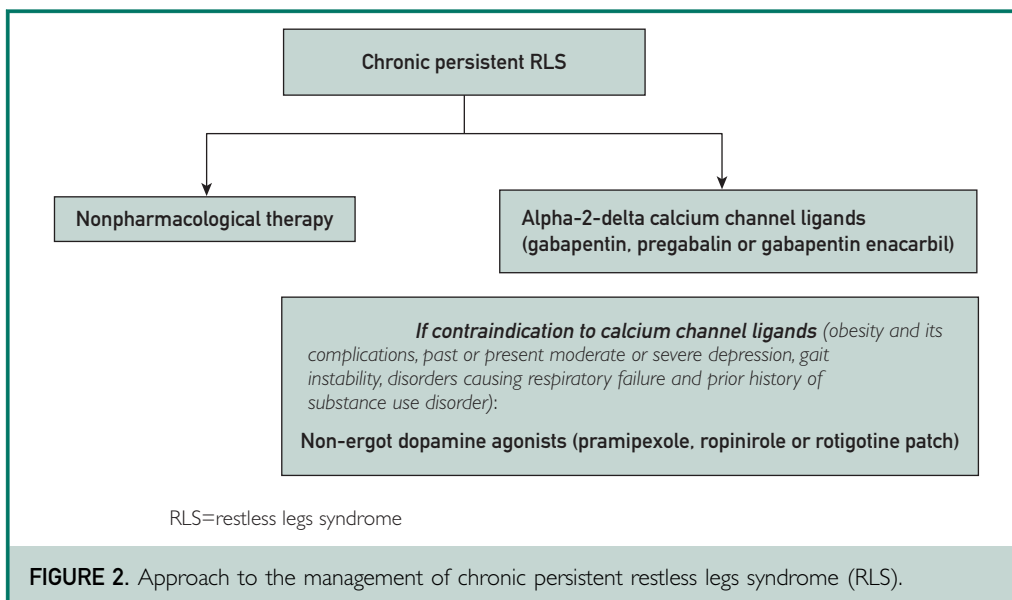
> ## Box 7. Management of Chronic Persistent RLS
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> - Treatment should start with an alpha$_2$-delta ligand (gabapentin, pregabalin, or gabapentin enacarbil) unless patient factors suggest that a nonergot dopamine agonist (pramipexole, ropinirole, or rotigotine patch) would be safer.
> - Factors favoring a dopamine agonist as initial treatment include obesity and its complications, past or present moderate or severe depression, gait instability, disorders causing respiratory failure, and previous history of substance use disorder. Alpha$_2$-delta ligands can worsen these conditions.
> - If untreated RLS is present for much of the day and night, consider the use of slow-release preparations (gabapentin enacarbil, unless a contraindication exists, then use the rotigotine patch).
> - If alpha$_2$-delta ligands are ineffective or poorly tolerated, change to a dopamine agonist.

of symptoms. Treatment should commence at 300 mg of gabapentin (100 mg in patients older than 65 years) or 75 mg of pregabalin daily (50 mg in patients older than 65 years) and be increased every few days as needed. Most RLS patients require 1200 to 1800 mg of gabapentin daily, but doses up to 3600 mg daily can be used. Because of nonlinear kinetics and substantial interindividual variability, the gabapentin dose often does not always reflect serum level, especially at single doses above 600 mg. For this reason, multiple doses of gabapentin, spaced at least 2 hours apart, may be necessary to enhance absorption and efficacy. Effective pregabalin doses are usually in the range of 150 to 450 mg daily. Gabapentin enacarbil is a prodrug of gabapentin, converted to gabapentin after absorption, and thus avoids the nonlinear pharmacokinetics of gabapentin. It is administered as a single daily dose of 600 mg (300 mg in patients older than 65 years) at 5 PM to target adequate therapeutic levels at bedtime. Doses of 1200 mg have been used. Class adverse effects include daytime drowsiness, dizziness, unsteadiness, and cognitive disturbances, all of which may be more frequent in older patients, as well as edema, weight gain, and depression, including suicidal ideation. The drugs have been reported to occasionally cause respiratory depression when they are used in patients with underlying pulmonary disease or in combination with opioids. Increased abuse potential has been reported in patients with a history of substance use disorder.[36] The development of adverse effects should be carefully monitored, especially if higher doses are used. Note that the alpha$_2$-delta ligands may provide additional benefit to RLS patients who have comorbidities of chronic pain, insomnia, or anxiety.

When dopamine agonists (Table 2) are used, nonergot agents should be prescribed because ergot agonists such as cabergoline and pergolide are associated with cardiac valvular fibrosis and other fibrotic reactions. Doses used are lower than approved for treatment of Parkinson disease because higher doses are associated with increased risk of augmentation. Pramipexole is usually commenced as 0.125 mg once daily, taken 2 hours before major RLS symptoms start. The dose is increased by 0.125 mg every 2 to 3 days until relief is obtained. The acceptable maximum daily dose is 0.5 mg in most

TABLE 1. Comparison of Alpha$_2$-Delta Ligands Used to Treat Restless Legs Syndrome			
	Gabapentin	Pregabalin	Gabapentin enacarbil
Time to maximum blood level	2 h	1.5 h	7-9 h
Elimination half-life	5-7 h	6 h	Relatively stable plasma levels during 18-24 h (elimination half-life, 6 h)
Metabolism and excretion	Renal	Renal	Intestinal metabolism; renal excretion
Initial daily dose	300 mg[a]	75 mg[a]	600 mg[a]
Maximum daily dose	3600 mg	450 mg	600 (-1200)[b] mg

[a]Doses should be adjusted for renal dysfunction. In patients older than 65 years, initial daily dose should be reduced (gabapentin, 100 mg; pregabalin, 50 mg; gabapentin enacarbil, 300 mg).
[b]Value in parentheses differs from Food & Drug Administration—approved value.

TABLE 2. Comparison of Dopamine Agonists Used to Treat Restless Legs Syndrome

	Pramipexole	Ropinirole	Rotigotine patch
Time to maximum blood level	2 h	1-1.5 h	Stable plasma levels during 24 h
Elimination half-life	8-12 h (increases with decreasing glomerular filtration rate and age)	6 h	Stable plasma levels during 24 h (elimination half-life biphasic, 3 h and 6 h)
Metabolism and excretion	Renal	Hepatic metabolism; renal excretion	Hepatic metabolism; renal excretion
Initial daily dose	0.125 mg	0.25 (-0.5)[a] mg	1 mg
Maximum daily dose	0.5 mg	(2-)[a] 4 mg	3 mg

[a]Values in parentheses differ from Food & Drug Administration—approved values.

patients. Ropinirole is usually commenced as 0.25 to 0.5 mg taken 1.5 hours before major symptoms start and is increased by 0.25 to 0.5 mg every 2 to 3 days. Most patients require 2 mg or less (note that 4 times higher equivalent doses are needed compared with pramipexole), but total daily doses up to 4 mg are FDA approved. Some patients require twice-daily doses of oral dopamine agonists, with an earlier dose in the late afternoon or early evening and a second dose 1 to 2 hours before bed. The rotigotine patch is applied once daily, commencing at 1 mg and increasing if necessary to 2 to 3 mg. Minor adverse effects of the agonists include nausea and light-headedness that usually resolve within 10 to 14 days. Daytime sleepiness may occur with higher doses, presenting as either sleep attacks closely following doses of the drug or continuous daytime sleepiness. Nasal stuffiness, constipation, insomnia, and leg edema occur less frequently and are reversible with cessation of treatment. Application site reactions commonly occur with the rotigotine patch.

Two major problems often limit the use of dopamine agonists, which is why they are not recommended as first-line agents unless there are contraindications to alpha$_2$-delta ligands. The single and by far most common problem is disease augmentation[37] (onset of RLS symptoms earlier in the day after an evening dose of medication, spread of symptoms to the arms, paradoxical worsening of symptoms with dose increase, and shorter effect of each dose of medication; Table 3). For pramipexole and ropinirole, this occurs in about 40% to 70% of patients during a 10-year period[38,39] or at an annual rate of 8% per year for at least the first 8 years of use. Augmentation frequency with the rotigotine patch may be slightly lower at 36% after 5 years.[40] The risk of augmentation is dose dependent, thus the great importance of not exceeding recommended maximum doses.

A second common adverse effect of long-term dopamine agonist use is impulse control disorder, with rate of occurrence estimated to be between 6% and 17%.[41] Before dopamine agonist therapy is commenced, patients should be questioned about a history of impulse control disorder, although the disorder may occur for the first time on starting the drugs. An impulse control disorder, which may be manifested as pathologic

TABLE 3. Diagnosis of RLS Augmentation With Dopaminergic Medication

1. Do RLS symptoms appear earlier than when the drug was first started?
2. Are higher doses of the drug now needed, or do you need to take the medicine earlier, to control the RLS symptoms compared with the original effective dose?
3. Has the intensity of symptoms worsened since starting the medication?
4. Have symptoms spread to parts of the body (eg, the arms) since starting the medication?

RLS, restless legs syndrome.
From Sleep Med.,[21] with permission.

FIGURE 3. Approach to the management of refractory restless legs syndrome (RLS).
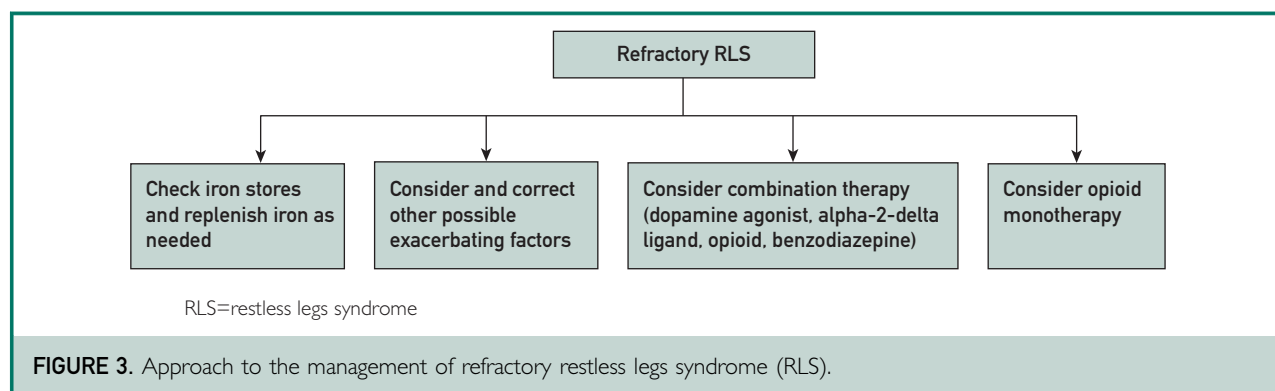
gambling, impulsive shopping, or hypersexuality,[41] commences an average of 9 months after introduction of the drug. Both these serious adverse effects should be assessed at every follow-up visit.

If augmentation is mild (predominantly manifested by symptoms starting less than 2 hours earlier in the day), consider initially splitting the dose with some of the drug administered at an earlier time. Use of extended-release pramipexole or ropinirole can be considered, generally without increasing the total daily dose, although limited data are available on their use in RLS. If an increase in total dose of dopamine agonist is deemed necessary, careful monitoring is essential to detect progressive augmentation. If augmentation progresses after the second increase in dose, another increase should not be made. Subsequent

choices include maintaining the dose, replacing oral agents with the rotigotine patch, adding another agent from a different class, and discontinuing the drug.

Discontinuation of dopamine agonists because of severe augmentation or other adverse effects and substitution of a drug of a different class (such as an alpha$_2$-delta ligand) can be achieved in 2 ways. The initial drug can be reduced slowly after the new agent is introduced with an overlap period when the patient is taking both medications. Alternatively, the initial drug can be reduced and discontinued with a drug holiday before the new agent is introduced. Higher doses of dopamine agonists should never be discontinued abruptly as serious withdrawal effects can occur, characterized by severe RLS, sleep disturbance, and depression. Rates of reduction should not exceed 0.25 mg (pramipexole) or 0.5 mg (ropinirole) every 3 days. Whereas a drug holiday can allow a new symptom baseline to be established, many patients with augmentation from dopamine agonists find it difficult to tolerate a period free of any medication, with exacerbation of RLS and profound insomnia lasting sometimes a week or longer after complete discontinuation.[42]

REFRACTORY RLS

Refractory RLS is restless legs unresponsive to monotherapy with tolerable doses of first-line agents due to reduction in efficacy, augmentation, or adverse effects (Figure 3; Box 8). (If apparent RLS has *never* responded to adequate doses of dopamine agonists

Box 8. Management of Refractory RLS

- Iron stores should be rechecked. If the serum ferritin level is less than 100 μg/L and symptoms are severe, intravenous iron therapy should be considered (see General Considerations).
- Other exacerbating factors should be sought. These include the use of medications that can worsen restless legs (see General Considerations); change in lifestyle, such as more sedentary behavior or shift work; and other causes of sleep disturbance, such as sleep apnea or chronic insufficient sleep.
- Consider combination therapy with drugs of different classes, taking into account adverse effects experienced during previous drug trials. Add a second agent and try to reduce the dose of the initial drug. Second agents may include a dopamine agonist for patients treated with an alpha$_2$-delta ligand or vice versa, a benzodiazepine (if RLS is present mainly at night with resulting insomnia), or a low- or high-potency opioid.
- Consider substituting an opioid such as oxycodone, hydrocodone, morphine, or methadone. In particular, consider low-dose methadone for severe refractory RLS resistant to other treatments.[39]

TABLE 4. Suggested Doses for Opioids in Restless Legs Syndrome

Drug	Starting total daily dose	Usual effective total daily dose
Tramadol (immediate release or ER)	50 mg (100 mg ER)	100-200 mg
Codeine	30 mg	60-180 mg
Morphine CR	10-15 mg	15-45 mg
Oxycodone (immediate release or ER)	5-10 mg	10-30 mg
Hydrocodone (immediate release or ER)	10-15 mg	20-45 mg
Methadone	2.5-5 mg	5-20 mg
Buprenorphine hydrochloride/naloxone (sublingual film or tablet)	0.5-1 mg	0.5-6 mg

CR, controlled release; ER, extended release.

administered at appropriate times, the accuracy of the diagnosis should be questioned.)

Opioids are highly effective in the management of refractory RLS,[16,43,44] reducing daytime tiredness and improving sleep and quality of life,[43,44] and thus should not be withheld from appropriately screened patients because of a fear of potential development of tolerance or dependence.[17] When opioids are used appropriately for RLS, escalation of dose is uncommon, and misuse is infrequent in the absence of a history of substance abuse. Nausea, constipation, and urinary retention are not uncommon but either resolve with time or can be managed symptomatically. Itch may be a problem as a result of mast cell degranulation rather than allergy. Daytime drowsiness, cognitive dysfunction, and unsteadiness resulting in falls, especially at night, are potential adverse effects. Opioids can suppress gonadotropin-releasing and luteinizing hormones, and symptoms related to low testosterone, such as lowered mood, increased sweating, and sexual dysfunction, may occur. Secondary adrenal insufficiency may be due to suppression of the hypothalamic-pituitary-adrenal axis. Opioids can induce central sleep apnea and may possibly precipitate or worsen obstructive sleep apnea. Testing for sleep apnea should be considered for RLS patients receiving opioids if there is a suspicion of sleep disordered breathing. In general, however, these medications are well tolerated at the low total daily recommended doses.

The choice of drug depends on physician preference, patient factors, and cost, and providers should familiarize themselves with the different characteristics of the various available medications. Initial use of short-acting agents is reasonable, but most patients transitioning to opioids will have augmented symptoms present for more than 12 hours per day, and thus long-acting drugs or extended-release formulations are most appropriate to avoid interdose rebound and to maintain benefit. Table 4 summarizes the doses of recommended opioids. The low total daily doses of opioids used for RLS rarely approach the higher doses used for the management of chronic pain.

Reasonable precautions should be taken in light of the opioid epidemic in the United States, and state regulations should be followed.[17] Patients should be questioned about risk factors for opioid abuse, including personal and family history of substance use

Box 9. Management of RLS During Pregnancy

- Nonpharmacologic therapies are strongly preferred, with special attention to moderate exercise and correction of iron stores by oral or, if necessary, intravenous administration of iron during the second or third trimester.
- Medications at lowest effective doses, used on demand if possible, should be reserved for severe RLS, preferably only in the second or third trimester to reduce any risk of inducing congenital abnormalities, and physicians should work closely with the patient's obstetric provider. The risk-benefit ratios of drugs in pregnancy should be carefully considered and discussed with each patient. Recommendations are based on 2 consensus publications.[45,46]

disorders, and an opioid contract should be signed by the patient. This should include information about drug adverse effects, the need for regular (usually every 3-6 months) follow-up visits, a notification that early prescription refill will generally not occur, and an understanding by the patient that prescriptions will be received from only a single provider and the dose will not be altered without permission. A urine drug screen should be considered at the start of therapy and at least yearly thereafter. State prescription drug monitoring databases should be regularly reviewed.

SPECIAL CIRCUMSTANCES

Pregnancy and Lactation
RLS may start or worsen during pregnancy, with a peak of incidence and severity in the third trimester. In general, symptoms improve or resolve around delivery, but women with pregnancy-related RLS have an increased risk for development of RLS in future pregnancies or later in life (Box 9).

Pregnancy. Clonazepam 0.25 to 0.5 mg before bed can be considered in the second and third trimesters. This drug should not be combined with antihistamines or anticonvulsants in pregnancy. Carbidopa/levodopa 25 mg/100 mg or 50 mg/200 mg controlled release can be considered. The alternative dopa decarboxylase inhibitor to carbidopa, benserazide, should not be used because of the risks of congenital malformations. Augmentation is common with levodopa, and patients should be monitored for this adverse effect. Oxycodone 5 to 10 mg before

bed can be considered for severe, refractory RLS in the second and third trimesters, but the neonate would need to be monitored for symptoms of opioid withdrawal.

Lactation. Clonazepam 0.25 to 0.5 mg and gabapentin 300 to 900 mg are possible options. For severe, refractory RLS, tramadol 50 to 100 mg can be considered. Dopamine inhibits prolactin production, and therefore levodopa and dopamine agonists should not be used during lactation.

Childhood
RLS is more difficult to diagnose in childhood, and careful attention should be paid to the child's own words in describing symptoms (Box 10). A strong family history in first-degree relatives may be helpful in doubtful cases. The presence of periodic limb movements during sleep on polysomnography may provide supportive diagnostic information. A relationship between RLS, periodic limb movements of sleep, and attention-deficit/hyperactivity disorder has been proposed.

Iron stores are lower in adolescents than in adults because of an increase in red cell mass during growth periods and, in women, the onset of menstruation. Thus, serum ferritin concentration is usually lower than in adults. Although optimal levels are uncertain, iron supplementation should be considered if the serum ferritin concentration is below 50 µg/L.[47] Oral ferrous sulfate 3 to 5 mg/kg in either tablet or liquid form should be administered once daily before breakfast. Constipation and abdominal discomfort are possible adverse effects. Serum ferritin concentration should be checked in 3 months to ensure that the level has risen above 50 µg/L.

If oral iron therapy is not tolerated or is not accompanied by a satisfactory rise in serum ferritin concentration, consideration can be given to intravenous administration of iron. Iron sucrose, 5 mg/kg to a maximum of 200 mg during 2 hours, has been reported effective in a case series.[48] Alternatively, ferric carboxymaltose, 10 mg/kg to a maximum of 1000 mg during 1 hour, may

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Box 10. Management of RLS in Childhood

- Nonpharmacologic approaches, including a consistent bedtime routine, avoidance of sleep deprivation, and elimination of caffeine, should be tried. If possible, selective serotonin reuptake inhibitors should be avoided.
- The mainstay of RLS treatment in children is iron replacement. Serum ferritin concentration should be measured; iron supplementation should be prescribed if levels are <50 µg/L.
- As in adults, first-line drug therapy in children should be alpha$_2$-delta ligands.
- Other drugs that can be considered include clonazepam, dopaminergic agents, and clonidine, but potential side effects should be carefully considered.

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be used. Potential side effects of intravenous administration of iron include subcutaneous extravasation with brownish skin discoloration, abdominal discomfort, and hypersensitivity reactions.

There are no large controlled trials of pharmacologic agents in childhood and no drugs approved by the FDA for RLS treatment in children. The following recommendations are therefore based on anecdotal experience and case series.[49,50] Gabapentin (5-15 mg/kg) and pregabalin (2-3 mg/kg) are first-line agents if iron is not needed or is ineffective. Second-line agents include clonazepam (0.1-1 mg), noting sedation and paradoxical hyperactivity as possible adverse effects. Dopamine agonists used in children include pramipexole (0.0625-0.25 mg), ropinirole (0.25-0.5 mg), and the rotigotine patch (1-3 mg), but they should preferably be avoided in adolescents because of the risk of precipitating schizophrenia in predisposed patients. If long-term therapy is contemplated, there is a significant risk for augmentation, and monitoring for impulse control disorders is important. Clonidine, an alpha$_2$-adrenergic agonist, can be considered in children (0.05-0.4 mg) who also have an anxiety disorder or attention-deficit/hyperactivity disorder. Its use may be limited by adverse effects including sedation, irritability, depression, and orthostatic hypotension.

Chronic Renal Insufficiency

RLS is common in patients with chronic renal insufficiency,[19,20] especially those undergoing hemodialysis. Iron status should be checked and managed with intravenous administration of iron or erythropoietin. Nonpharmacologic therapies, including aerobic exercise and the use of vitamins C and E, may be beneficial. Ropinirole and rotigotine, both with hepatic metabolism, can be used. Gabapentin and pregabalin are also effective, but owing to renal metabolism, doses should be kept low and patients carefully monitored for adverse effects, such as mental confusion and falls.[51] RLS often improves or resolves after renal transplant.

ALTERNATIVE, INVESTIGATIVE, AND POTENTIAL FUTURE THERAPIES

Many other therapies, usually based on anecdotes, open-label series, or small controlled trials, have been proposed.[52] In assessing the efficacy of such therapies, the strong effect of placebos in improving RLS should be carefully weighed.

Mechanical Devices

Limited evidence in support of the use of pneumatic compression devices is based on a single small controlled trial.[53] Vibration devices do not improve RLS symptoms but may enhance the quality of sleep in RLS patients.

Electrical and Magnetic Stimulation

Case reports have suggested partial benefit of spinal cord stimulation by implanted electrodes, mainly in patients with chronic pain in addition to RLS. Transcutaneous spinal cord stimulation with direct current showed improved RLS symptoms compared with sham stimulation up to an hour after 15 minutes of treatment in one series.[54] Transcranial and local leg electrical stimulation has not been effective. Deep brain stimulation targeting various regions, largely for control of Parkinson disease, has produced variable effects on RLS. Transcranial magnetic stimulation has also produced variable results.

Botulinum Toxin

There are conflicting reports on the effects of botulinum toxin injection into leg muscles, with no convincing evidence of long-term benefit.[55,56]

Cannabis

No controlled clinical trials have evaluated the use of cannabis for RLS. A case series from a single center and patient anecdotes suggest the possibility of some benefit,[57] but the formulation, dosage, and mode of administration that might be beneficial are unclear. Anecdotal experience suggests that ingested cannabis (brownies, cookies, or other edibles) is ineffective, whereas inhaled cannabis (cannabis cigarette or vaporizer)

may, in some patients, provide rapid but short-lived relief of RLS symptoms.

Cannabis can interact both pharmacokinetically and pharmacodynamically with multiple other drugs that are used to treat RLS, including dopamine agonists, alpha₂-delta ligands, and benzodiazepines, potentially increasing adverse effects from these agents.[58] Inhaled cannabis may be harmful in patients with lung disorders, such as asthma or chronic obstructive pulmonary disease. The long-term adverse effects or complications of cannabis are unknown. Despite that cannabis is legal in many states, it is still illegal under federal law in the United States.

Minerals and Vitamins

Other than for iron, there is no evidence that supplemental minerals or vitamins relieve idiopathic RLS. Specifically, there is no evidence to support magnesium supplementation.[59] A single controlled trial suggested benefit of vitamin C and vitamin E in uremic RLS patients.[60]

In summary, the management of RLS continues to evolve as new treatment modalities become available and older ones are prescribed less frequently. Basic science studies to better understand the pathophysiologic mechanism of RLS will, with time, lead to the exploration of novel therapeutic agents.[61] Further research is needed to understand the augmentation phenomenon associated with dopaminergic agents and to determine how best to reduce or to avoid it. Long-term follow-up studies of the alpha₂-delta ligands and opioids are needed. Older studies suggested the efficacy of carbamazepine, but antiseizure medications, other than the alpha₂-delta ligands, are not commonly used in clinical practice. Studies of newer anticonvulsants should be undertaken. Further studies of clonidine would help delineate its role in RLS.[62] Controlled studies of drugs that increase adenosine[63] or decrease glutamine[64] might open up new approaches to RLS therapy. Because serum measurements of iron status do not correlate with brain iron concentrations, markers of intracerebral iron deficiency associated with response to intravenous iron therapy, such as quantitative transcranial sonography of the substantia nigra,[65] need to be developed and tested. Noninvasive electrical stimulation techniques need further exploration, especially transcutaneous spinal stimulation.

CONCLUSION

The management of RLS has steadily advanced during the past few decades, resulting in increased relief for patients with this distressing disorder. In the previous iterations of this algorithm, we stated that further revisions will be needed in the future as our understanding of RLS grows and new approaches to treatment are developed. This is undoubtedly again true in 2021.

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Abbreviations and Acronyms: **FDA =** Food and Drug Administration; **RLS =** restless legs syndrome

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