An Algorithm for the Management of Restless Legs Syndrome

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Restless legs syndrome (RLS) is a common disorder with a prevalence of 5% to 15%. Primary care physicians must become familiar with management of this disorder. This algorithm for the management of RLS was written by members of the Medical Advisory Board of the Restless Legs Syndrome Foundation and is based on scientific evidence and expert opinion. Restless legs syndrome is divided into intermittent, daily, and refractory types. Nonpharmacological approaches, including mental alerting activities, avoiding substances or medications that may exacerbate RLS, and addressing the possibility of iron deficiency, are discussed. The role of carbidopa/levodopa, dopamine agonists, opioids, benzodiazepines, and anticonvulsants for the different types of the disorder is delineated.

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CR = controlled release; MAB = medical advisory board; RLS = restless legs syndrome

Restless legs syndrome (RLS) is characterized by an urge to move the legs, usually associated with limb discomfort.[1] The symptoms occur at rest, are relieved by movement, and are worst in the evening and at night. Restless legs syndrome is usually associated with involuntary contractions of the legs during sleep, known as periodic limb movements. The severity of symptoms ranges from annoying and infrequent to distressing and daily. For many patients, RLS is a cause of disabling sleep onset or maintenance insomnia. The disorder is common, with previous estimates of prevalence ranging from 5% to 15%.[2-4] A recent report suggested a prevalence at one primary care practice of 6% for symptoms described as at least mildly distressing and occurring 3 or more times a week.[5] Restless legs syndrome is familial in about 50% of patients[6] but may be idiopathic or related to acquired conditions, especially iron deficiency and chronic renal failure. Several medications have been shown to be effective in treating RLS.[7] The high prevalence of RLS requires that primary care physicians familiarize themselves with the condition and take a leading role in its management.

Two rigorous evidence-based reviews of the treatment of RLS have been published under the auspices of the Standards of Practice Committee of the American Academy of Sleep Medicine.[7,8] Although evidence-based reviews are valuable, they do not necessarily tell the whole story. 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, few if any large comparative studies of different drugs have been published. Large controlled trials usually test short-term use of drugs, and long-term studies generally provide lower levels of evidence, being either uncontrolled prospective or retrospective studies. Nevertheless, data on continued use of medication in the community may be highly relevant for medical practice. For many of these reasons, evidence-based reviews generally make authoritative statements on the degree of evidence in support of the use of each medication for a defined disorder, but they are 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 managed predominantly by specialists with considerable experience and a reasonable knowledge of the published literature, evidence-based reviews may be sufficient. However, for

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A question-and-answer section appears at the end of this article.

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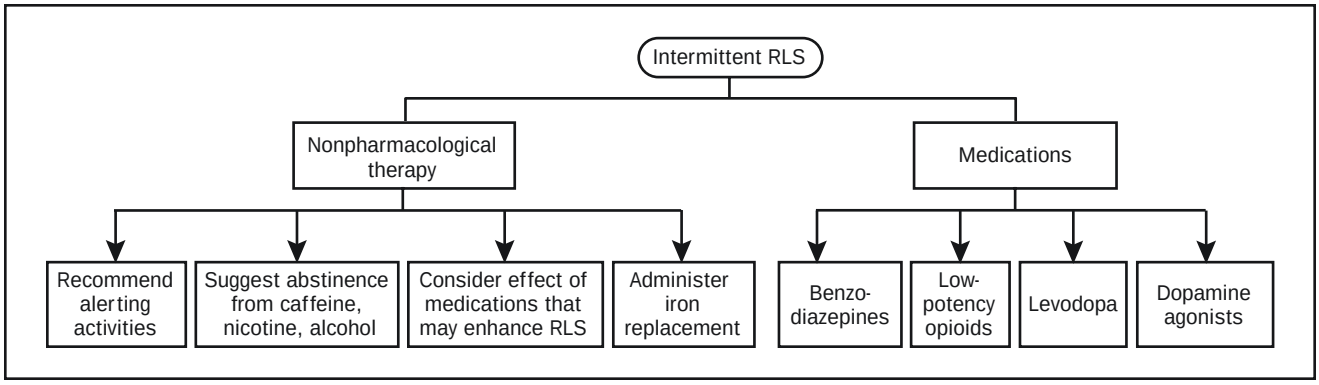

FIGURE 1. Algorithm for the management of intermittent restless legs syndrome (RLS).

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

These considerations led the medical advisory board (MAB) of the nonprofit Restless Legs Syndrome Foundation to attempt the construction of an algorithm for the management of RLS. The effort was supported by the Board of Directors of the Restless Legs Syndrome Foundation, but this article is entirely the work of the physicians and scientists on the MAB. A task force of the MAB 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 in either academic or primary care settings and have conducted original research on this disorder. Some have been members of task forces that have produced the previously discussed evidence-based reviews.

Previous attempts at algorithms have been published,[9-12] but to our knowledge, this is the first consensus approach developed by a group of RLS specialists. It is based on both a detailed knowledge of the literature, including evidence-based assessments, and expert opinion from practical experience. 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 in the United States. Different medications are available in other countries, and this algorithm may not be applicable internationally. Obviously, 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 has not approved any medication for the treatment of RLS, and thus all the 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.

INTERMITTENT RLS

Intermittent restless legs syndrome is defined as RLS that is troublesome enough when present to require treatment but does not occur frequently enough to necessitate daily therapy (Figure 1).

Nonpharmacological Strategy

A nonpharmacological approach involves the following:

- Consider determining the serum ferritin level. If the serum ferritin level is low, administer iron replacement (see subsequent comment 1)
- 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, nicotine, and alcohol
- 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 (see subsequent comment 2)

Comments

1. Because RLS may be the only clinical indication of iron deficiency, clinicians should consider determining the serum ferritin level in all patients with RLS, especially those with a history of gastrointestinal blood loss, disorders or medications predisposing to gastrointestinal blood loss, menorrhagia, frequent blood donation, or recent onset or worsening of symptoms. If the serum ferritin concentration is in the abnormal range for the specific

laboratory (usually <20 μg/mL) or percent iron saturation is low, a cause of iron deficiency should be pursued and replacement treatment instituted. A serum ferritin concentration lower than 45 to 50 μg/mL has been associated with an increased severity of RLS,[13,14] and therapy can be attempted in patients with levels in this range on a case-by-case basis. A common regimen is 325 mg of ferrous sulphate 3 times a day in combination with 100 to 200 mg of vitamin C with each dose to enhance absorption. Oral iron therapy can cause constipation and abdominal discomfort, and the dose may need to be reduced in some patients. Iron tablets should ideally be taken on an empty stomach to enhance absorption, but if gastrointestinal symptoms develop, they should be taken with food. 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 50 μg/mL and percent iron saturation is greater than 20%. Iron therapy can then be discontinued, but follow-up serum ferritin determinations are recommended to ensure that levels do not decrease, especially if RLS symptoms worsen. Of note, RLS does not always respond to an increasing serum ferritin concentration, even if it was low initially.

2. Clinical experience suggests that most antidepressants may sometimes be associated with initiation or worsening of RLS. However, if antidepressants are deemed necessary, the symptoms can usually be treated in the same way as primary RLS. Alternatively, use of bupropion can be considered because this antidepressant has been shown to reduce periodic limb movements in depressed patients and thus may be less likely to induce or worsen RLS.[15]

Medication

Intermittent use of the following medications may be helpful:

- Carbidopa/levodopa, 25 mg/100 mg, or controlled release (CR), 25 mg/100 mg (see subsequent comment 3)
- Dopamine agonists, such as pramipexole or ropinirole (see subsequent comment 4)
- Low-potency opioids, such as propoxyphene or codeine, or opioid agonists, such as tramadol (see subsequent comment 5)
- Benzodiazepines or benzodiazepine agonists, such as temazepam, triazolam, zolpidem, or zaleplon (see subsequent comment 6)

Comments

3. Carbidopa/levodopa, 25 mg/100 mg (1/2-1 tablet), can be used for RLS that occurs intermittently in the evening, at bedtime, or on waking during the night or RLS associated with specific activities, such as airplane or lengthy car rides or theater attendance. Controlled-release 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 CR 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.[7,8] For maximal absorption, levodopa should not be taken with high-protein foods.

Problems with levodopa treatment include augmentation and rebound. *Augmentation* is defined as a worsening of RLS symptoms earlier in the day after an evening dose of medication, including earlier onset of symptoms, increased intensity of symptoms, or spread of symptoms to the arms.[16] Up to 70% of patients taking levodopa daily will develop augmentation, and the risk increases with daily doses of 200 mg or more.[17] The risk of augmentation may be lower with intermittent use, such as fewer than 3 times a week, but this has not been established firmly. Patients should be warned about the phenomenon because taking additional doses of levodopa results in worsening augmentation. If augmentation occurs, the drug should be discontinued and another agent substituted. *Rebound*, the recurrence of RLS in the early morning, occurs in 20% to 35% of patients taking levodopa.[17,18]

4. The action of dopamine agonists generally commences 90 to 120 minutes after ingestion; thus, these agents cannot be used effectively once symptoms have started. For dosage schedules, see comment 7 discussed subsequently.

5. Intermittent use of low-potency opioids or opioid receptor agonists, usually before bed, can be effective. Doses of 100 to 200 mg of propoxyphene napsylate; 65 to 130 mg of propoxyphene hydrochloride; 30 to 60 mg of codeine, usually available 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.

6. Intermittent use of benzodiazepines or benzodiazepine receptor agonists before sleep may be useful, especially if the patient has another cause of poor sleep in addition to RLS, such as psychophysiologic insomnia. Short-acting agents, such as triazolam (0.125-0.5 mg), 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), may be helpful for RLS that awakens the patient later in the night. Most controlled trials have been performed with clonazepam.[7] Although some investigators have shown this drug to be well tolerated in older patients,[19] its long

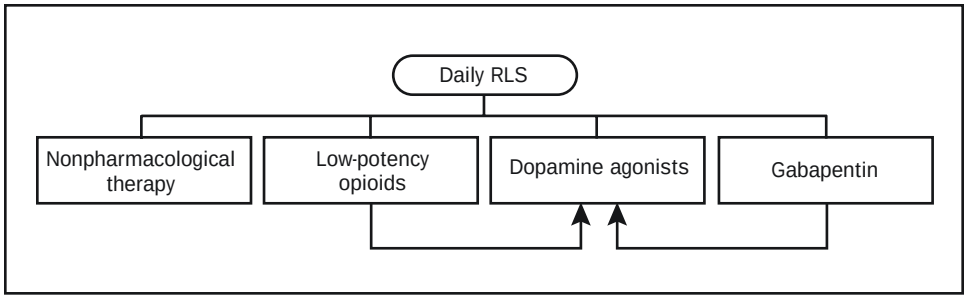

FIGURE 2. Algorithm for the management of daily restless legs syndrome (RLS). Dopamine agonists are the treatment of choice in most patients. Low-potency opioids and gabapentin are alternatives, but dopamine agonists should be used if they are unsuccessful.

duration of action may result in more adverse effects, such as unsteadiness during the night and drowsiness or cognitive impairment in the morning.

DAILY RLS

Daily restless legs syndrome is defined as RLS that is frequent and troublesome enough to require daily therapy (Figure 2).

Nonpharmacological Strategy

The nonpharmacological approach for daily RLS is the same as for mild RLS.

Medication

- Dopamine agonists, such as pramipexole or ropinirole (see subsequent comment 7)
- Gabapentin (see subsequent comment 8)
- Low-potency opioids, such as propoxyphene or codeine, or opioid agonists, such as tramadol (see subsequent comment 9)

Comments

7. Dopamine agonists are the drugs of choice in most patients with daily RLS.[7,8,20,21] The nonergot agonists such as pramipexole and ropinirole are generally preferred to the ergot agonists such as pergolide because of their more favorable adverse-effect profile. 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. Most patients require 0.5 mg or less, but doses up to 2 mg may be needed. Ropinirole is usually commenced as 0.25 mg at the same time as pramipexole in relationship to symptoms and is increased by 0.25 mg every 2 to 3 days. Most patients require 2 mg or less (note that higher equivalent doses are needed compared with pramipexole), but doses up to 4 mg or higher may be needed. Some patients require twice-daily doses of agonists, with an earlier dose in the late afternoon or early evening and a second dose before bed.

Augmentation is less common with these drugs than with levodopa but may occur in about one third of patients taking pramipexole for 2 years.[22,23] Equivalent data for ropinirole are not available. In contrast to levodopa, augmentation can usually be managed in many patients, at least initially, by additional doses of the drug earlier in the day. An alternative approach is to switch to another medication. Adverse effects of the agonists include nausea and light-headedness that usually resolve within 10 to 14 days. Nasal stuffiness, constipation, insomnia, and leg edema occur less frequently and are reversible with cessation of treatment. Hypersomnia appears less common than when the drugs are used to treat Parkinson disease,[24] perhaps because of the lower doses used.

8. Gabapentin may be an alternative choice, particularly in less intense RLS, RLS perceived as painful, RLS in combination with a painful peripheral neuropathy or an unrelated chronic pain syndrome, or RLS in association with neurodegenerative disorders such as Parkinson disease or dementia. Unless RLS occurs throughout most of the day, gabapentin should be used as once- or twice-daily doses in the late afternoon or evening or before sleep. Treatment should commence at 100 to 300 mg per dose because of the tendency of the drug to cause somnolence and gait unsteadiness, especially in elderly patients. A controlled trial has suggested that mean doses of 1300 to 1800 mg/d are needed for efficacy,[25] but many patients appear to benefit from lower doses. If gabapentin is unsuccessful or poorly tolerated, a dopamine agonist should be considered next, if not already tried.

9. Low-potency opioids may be an alternative choice. (See comment 5 for dosage schedules.) If low-potency opioids are unsuccessful, use of a dopamine agonist should be considered, if not already tried.

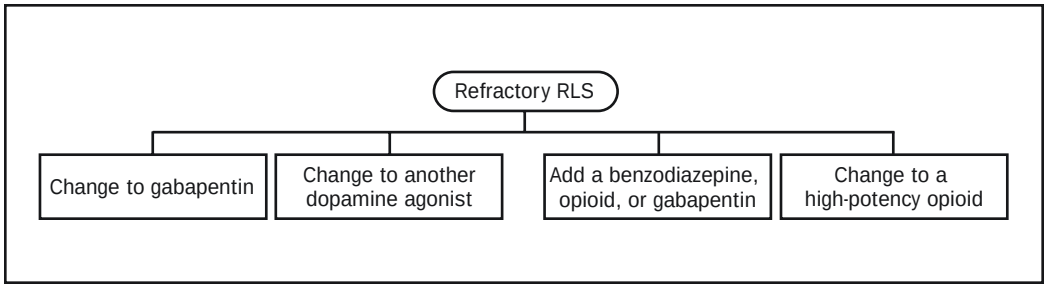

FIGURE 3. Algorithm for the management of refractory restless legs syndrome (RLS).

REFRACTORY RLS

Refractory restless legs syndrome is defined as daily RLS treated with a dopamine agonist with 1 or more of the following outcomes:

- Inadequate initial response despite adequate doses
- Response that has become inadequate with time, despite increasing doses
- Intolerable adverse effects
- Augmentation that is not controllable with additional earlier doses of the drug (Figure 3)

MEDICATIONS

Four different approaches can be tried. A referral to a specialist in RLS management should be considered.

- Change to gabapentin (see subsequent comment 10)
- Change to a different dopamine agonist (see subsequent comment 11)
- Add a second agent such as gabapentin, a benzodiazepine, or an opioid (see subsequent comment 12)
- Change to a high-potency opioid or tramadol (see subsequent comment 13)

COMMENTS

10. See previous comment 8 on gabapentin.

11. Patients often show different responses to other dopamine agonists when a suboptimal response has been obtained with one agent. Adverse effects and efficacy may vary, and the development of augmentation with one agent does not necessarily predict augmentation with a different drug, at least initially.[22] Ropinirole or pramipexole can be substituted for each other, and occasionally pergolide can be used, although adverse effects are generally more frequent, including rare reports of ergotlike fibrosing reactions. A dose of 0.05 mg of pergolide is equivalent to 0.125 mg of pramipexole, and most patients respond to a daily dose of about 0.2 mg. If augmentation develops with a second dopamine agonist, a change to a different class of agents is mandatory.

12. See previous comments 6, 8, and 9. Long-term use of benzodiazepines may lead to dependency, but these drugs should not be withheld in appropriate patients. Usually, the initial agent is continued at the same dose, but it may be possible to reduce the dose with time.

13. High-potency opioids may be highly effective in the management of RLS and should not be withheld from appropriate patients because of a fear of potential development of tolerance or dependence. Escalation of doses is uncommon, and dependence is infrequent in the absence of a history of substance abuse. Nausea and constipation may occur. Controlled trials have shown efficacy with oxycodone.[7] Drugs that have been used include oxycodone (5-15 mg), hydrocodone (5-15 mg), methadone (5-10 mg), and tramadol (50-100 mg), but other equivalent opioids may be considered. Opioids can be used 1 to 3 times a day depending on the timing of symptoms. Sustained-release opioid preparations may be appropriate in some patients.

ALTERNATIVE, INVESTIGATIVE, AND POTENTIAL FUTURE THERAPIES

The management of RLS continues to evolve as new drugs become available and older ones are prescribed less frequently. Carbamazepine and clonidine have been used successfully in controlled trials[7] but are not commonly used in clinical practice. Among potential new dopamine agonists, cabergoline is of interest[26] because of its long half-life of 65 hours, which theoretically might produce less augmentation. Magnesium has been reported as an effective therapy for RLS in a small open-label trial.[27] Iron is not well absorbed in the gastrointestinal tract, and thus the treatment of RLS with intravenous iron infusions is currently being investigated in patients with both low and normal serum ferritin concentrations.[28] Of note, the first report of success with intravenous iron therapy dates back more than 50 years.[29] This algorithm will undoubtedly need revision in the future as our understanding of RLS grows and new pharmacological agents are developed.

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Questions About RLS

1. Which <u>one</u> of the following should be the <u>goal</u> for the serum ferritin concentration for optimal control of RLS?

   a. >100 μg/mL
   b. >50 μg/mL
   c. >30 μg/mL
   d. >20 μg/mL
   e. >10 μg/mL

2. Which <u>one</u> of the following daily doses of pramipexole is the <u>initial</u> dose for the management of RLS?

   a. 0.125 mg
   b. 0.5 mg
   c. 1 mg
   d. 1.5 mg
   e. 2 mg

3. A patient with RLS taking 2 tablets of carbidopa/levodopa (25 mg/100 mg) before bed has worsening RLS during the afternoon and evening. Which *one* of the following is the *most optimal* strategy?
   a. Add another dose of carbidopa/levodopa at 3 PM
   b. Change the timing of the same dose of carbidopa/levodopa to 3 PM
   c. Continue carbidopa/levodopa before bed but add a dose of pramipexole or ropinirole at 3 PM
   d. Continue carbidopa/levodopa before bed but add a dose of gabapentin at 3 PM
   e. Discontinue carbidopa/levodopa and substitute a dose of pramipexole or ropinirole 2 hours before bed

4. A previously untreated patient presents with daily RLS commencing at 9 PM and preventing sleep onset for 2 to 3 hours each night. Which *one* of the following is the *most appropriate* medication to prescribe initially?
   a. Amitriptyline
   b. Carbidopa/levodopa
   c. Clonazepam
   d. Oxycodone
   e. Ropinirole

5. A 55-year-old patient with painful lower extremity paresthesias caused by diabetic peripheral neuropathy presents with an uncontrollable urge to move his legs in bed at night. This is relieved by walking but delays sleep onset by several hours. Which *one* of the following is the *most appropriate* medication to prescribe initially?
   a. Carbidopa/levodopa
   b. Clonazepam
   c. Gabapentin
   d. Nortriptyline
   e. Oxycodone

Correct answers:
1. *b*, 2. *a*, 3. *e*, 4. *e*, 5. *c*