Pharmacologic and Nonpharmacologic Treatment of Restless Legs Syndrome

Galia V. Anguelova, MD, MSc, Monique H.M. Vlak, MD, PhD, Arthur G.Y. Kurvers, MD, Roselyne M. Rijsman, MD, PhD*

KEYWORDS

• Restless legs syndrome • Therapy • Treatment • Pharmacologic • Nonpharmacologic • Augmentation

KEY POINTS

- There is limited evidence for nonpharmacologic treatment in primary restless legs syndrome (RLS): pneumatic compression, near-infrared light spectroscopy, and transcranial magnetic stimulation.
- In moderate to severe RLS, pharmacologic treatment may be considered, starting with iron supplementation if applicable.
- There is strong evidence for both $\alpha 2\delta$ ligands and dopamine agonists in the therapy for RLS.
- When single-drug therapy with an $\alpha 2\delta$ ligand or dopamine agonist is insufficient, a combination of both may be considered or oxycodone/naloxone.
- To treat augmentation, a low dose or longer-acting dopaminergic drug may be chosen, or a switch to an $\alpha 2\delta$ ligand or oxycodone/naloxone may be considered.

INTRODUCTION

Restless legs syndrome (RLS) is a sleep-related disorder defined by an urgency to move the legs, usually combined with uncomfortable or unpleasant sensations, which occurs or worsens during rest, usually in the evening or at night, and disappears with movement of the legs.[1] It occurs in 5% to 15% of European and North American adults, 2% to 3% with moderate to severe symptoms, twice as often in women as in men, and has a mean onset age between 30 and 40 years.[1] RLS can be classified as idiopathic or primary, and secondary to comorbid conditions (eg, renal disease, polyneuropathy).[1] The pathophysiology of RLS is still unclear. However, dopaminergic dysfunction and iron deficiency have been suggested to play an essential role, possibly interacting with each other as well.[1] Glutamate, adenosine, and opiate systems are also considered to play a role in the pathophysiology.[1] This article provides an updated practical guide for the treatment of primary RLS in adults. Iron deficiency is included in our definition of primary RLS because of its essential role in the pathophysiology. Treatment of periodic limb movements was beyond the focus of this article. The available evidence is reviewed for pharmacologic as well as nonpharmacologic treatment options.

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Center for Sleep and Wake Disorders, Haaglanden Medical Center, The Hague, The Netherlands
* Corresponding author. Center for Sleep and Wake disorders, Haaglanden Medical Center, PO 432, The Hague 2501 CK, The Netherlands.
E-mail address: r.rijsman@haaglandenmc.nl

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METHODS

This article was written in continuation of the 2016 RLS guidelines by the American Academy of Neurology (AAN).[2] The authors performed a PubMed search for articles on treatment of primary RLS using MeSH (Medical Subject Headings) terms and keywords with a start date of 1 January 2015, because the AAN guideline included articles published until the 15 July 2015.[2] Our search was last performed on 15 October 2017. Details on the search strategy are given in **Box 1**.

The titles and abstracts of the eligible articles were screened. The authors only included studies that met the following criteria: (1) original article; (2) on treatment of primary RLS (including iron deficiency–related RLS); (3) in humans; (4) published in English. Case reports were excluded. We focused primarily on the effect on RLS symptoms and periodic limb movements. A standardized tool to report RLS symptom severity is the International Restless Legs Syndrome Study Group rating scale (IRLS), which measures symptoms in the past week with 10 items each graded from 0 to 4 with increasing severity (with a maximum score of 40).[2] Because international guidelines no longer recommend the use of pergolide for RLS, we did not include new studies on pergolide alone. Acupuncture, Chinese herbs, meditation, music, and prayer were considered outside the scope of our review.

Additional articles found in the references of articles identified through our database search were also reviewed if considered relevant according to the criteria mentioned earlier. Relevant articles were classified according to their risk of bias (increasing from I to IV) and subsequent recommendations were made according to the criteria described by the AAN guideline (level A, B, C, and U in decreasing order of evidence level).[2] Studies published after the 2016 AAN guideline are discussed in detail. For studies already described in the 2016 AAN guideline, we refer to the AAN guideline.

RESULTS

Pharmacologic Treatment Options

Table 1 shows the pharmacologic agents effective in RLS treatment with at least evidence level C with their initial and usual daily dose, pharmacokinetics, specific considerations, and side effects.

Dopamine precursors

Levodopa Levodopa was one of the first drugs studied for treating RLS. There are 4 class III studies showing a benefit of levodopa (100–200 mg) on RLS severity (level C).[2] Also a possible effect on the periodic limb movement index (PLMI) was found based on 3 class III studies (level C).[2] Augmentation (discussed later) is a major problem with long-term daily use of levodopa in RLS. It occurs in 40% to 60% of patients after 6 months of follow-up, but augmentation rates as high as 71% have been reported.[3]

Non–ergot-derived dopamine agonists

Pramipexole Pramipexole is a dopamine agonist which is excreted by the kidney. There is level A evidence that pramipexole improves RLS symptoms based on 3 class I studies and 6 class II studies.[2] Improvement of PLMI was seen in 3 class II studies giving level B evidence.[2] Two open-label studies reported that efficacy on RLS symptoms continues up to 1 year.[4,5] A study comparing pramipexole with dual-release levodopa/benserazide found that both drugs are effective in reducing RLS symptoms and PLMI, but levodopa had a higher rate of augmentation (21%) compared with pramipexole (6%).[6]

Ropinirole Ropinirole was effective in improving RLS symptoms up to 6 months according to 2 class I studies and up to 1 year according to 2 class I studies (level B).[2] Ropinirole also improves PLMI according to 2 class I studies (level A).[2] Ropinirole is a dopamine agonist primarily metabolized by the liver, mainly via the cytochrome P (CYP) 1A2 enzyme but also via CYP3A. Substances that inhibit and promote those enzymes can interact with ropinirole.[7]

Rotigotine Rotigotine is a dopaminergic agonist delivered through a transdermal patch allowing a continuous release and thus maintaining stable concentrations that mimic physiologic striatal dopamine receptor function.[8–10] Because of the transdermal delivery, rotigotine is especially useful in patients with daytime symptoms, patients with swallowing difficulties, and patients undergoing surgery.[11] Rotigotine has been shown to reduce RLS symptoms up to 6 months in 2 class I and 3 class II studies (level A) and reduce PLMI in 1 class I study (level B).[2] Our search strategy identified 1 new class I study that has been published since the AAN guideline in 2016.[12] This study randomized 150 patients to receive an optimal dose of rotigotine (1–3 mg) or placebo (randomization 2:1). Although rotigotine was effective in improving IRLS scores at 4 weeks of treatment, there was no superiority compared with placebo (least square mean with 95% confidence intervals [CIs] from an ANCOVA [Analysis of Covariance] model −0.27, 95% CI, −3.0–2.4; $P = .8451$). Long-term efficacy was studied in 3 noncomparative