AMERICAN ACADEMY OF NEUROLOGY®

Summary of Evidence-based Guideline for **Clinicians**

Practice Guideline: Treatment of Restless Legs Syndrome in Adults

This is a summary of the American Academy of Neurology (AAN) guideline, "Treatment of restless legs syndrome in adults," which was published in *Neurology*® online on November 16, 2016, and appears in the December 13, 2016, print issue.

Please refer to the full guideline at *AAN.com/guidelines* for more information, including the definitions of the classifications of evidence and recommendations.

In moderate to severe primary restless legs syndrome (RLS), clinicians should consider prescribing a pharmacologic agent to reduce RLS symptoms:

Strong Evidence	Pramipexole, rotigotine, cabergoline*, and gabapentin enacarbil (**Level A**).
Moderate Evidence	Ropinirole, pregabalin, and IV ferric carboxymaltose, and in patients with serum ferritin ≤ 75 mcg/l, ferrous sulfate with vitamin C (**Level B**).
Weak Evidence	Levodopa (**Level C**).
	Cabergoline* instead of levodopa (**Level C**).
Insufficient Evidence	Preferential use of pregabalin instead of pramipexole (**Level U**).
	Gabapentin, IV iron sucrose, oxycodone, clonazepam, bupropion, clonidine, selenium, rifaximin, botulinum neurotoxin, valproic acid, carbamazepine, or valerian in the treatment of RLS (**Level U**).

* Cabergoline is rarely used in clinical practice for RLS because of a risk of cardiac valvulopathy at higher doses.

For patients with RLS who have not responded to other treatments:

Weak Evidence	Prolonged-release oxycodone/naloxone (where available) (**Level C**), but potential benefits need to be weighed against known opioid risks.

For patients with primary RLS for whom clinicians want to target sleep, clinicians should consider prescribing a pharmacologic agent that improves objective or subjective sleep parameters (or both). Evidence supports agents to different extents for subjective and objective outcomes:

Strong Evidence	Ropinirole, when targeting periodic limb movements of sleep (PLMS), specifically the Periodic Limb Movement Index (PLMI) as measured by polysomnography (PSG) (**Level A**).
	Cabergoline* and gabapentin enacarbil, with regard to subjective sleep measures (**Level A**).
Moderate Evidence	Pramipexole, rotigotine, cabergoline*, and pregabalin, when targeting PLMS, specifically the PLMI as measured by PSG (**Level B**).
	Ropinirole, gabapentin enacarbil, and pregabalin, for at least some objective sleep measures (e.g., total sleep time [TST], sleep efficiency, sleep latency, and wake after sleep onset [WASO]) (**Level B**).
	Pregabalin instead of pramipexole, with regard to subjective sleep outcomes (**Level B**).
	Ropinirole, pramipexole, and pregabalin, with regard to subjective sleep measures (**Level B**).
Moderate to Weak Evidence	Rotigotine, with regard to subjective sleep measures (**Levels B** and **C**).

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Weak Evidence	Levodopa, when targeting PLMS, specifically the PLMI as measured by PSG (**Level C**).
	Pramipexole in preference to pregabalin, when targeting PLMS, specifically the PLMI as measured by PSG (**Level C**).
	Pregabalin in preference to pramipexole, with regard to objective sleep measures other than PLMI (e.g., TST, sleep efficiency, sleep latency, and WASO) (**Level C**).
	Levodopa, with regard to subjective sleep measures, with the strength of evidence varying by measure and, sometimes, dose (**Level C**).
Insufficient Evidence	Gabapentin enacarbil, IV ferric carboxymaltose, or IV iron sucrose, when targeting PLMS, specifically the PLMI as measured by PSG (**Level U**).
	Pramipexole, rotigotine, cabergoline*, or levodopa, with regard to other objective sleep measures (e.g., TST, sleep efficiency, sleep latency, and WASO) (**Level U**).
	Ferric carboxymaltose, with regard to subjective sleep measures (**Level U**).

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For patients with RLS for whom clinicians want to target concomitant psychiatric symptoms:

Moderate Evidence	Ropinirole, in the context of anxiety **(Level B**).
	Gabapentin enacarbil, for overall mood (**Level B**).
Weak Evidence	Ropinirole, in the context of depression (**Level C**).
	Pramipexole, for depression and anxiety, in the context of moderate to severe RLS-related mood disturbance (**Level C**).

For patients with RLS for whom clinicians want to select an agent that improves QoL:

Moderate Evidence	Ropinirole, pramipexole, cabergoline*, gabapentin enacarbil, or IV ferric carboxymaltose (**Level B**).
Weak Evidence	Rotigotine or pregabalin (**Level C**).
Insufficient Evidence	Levodopa, for improving QoL in RLS (**Level U**).

* Cabergoline is rarely used in clinical practice for RLS because of a risk of cardiac valvulopathy at higher doses.

When avoidance of augmentation is a deciding factor:

Weak Evidence	Pregabalin rather than pramipexole, when considering 52-week treatment in light of lower augmentation rates with pregabalin (**Level C**).
	Cabergoline* rather than levodopa, when considering 30-week treatment in light of lower augmentation rates with cabergoline (**Level C**).
Insufficient Evidence	Which dopaminergic agents cause the least augmentation because augmentation rates are most commonly reported in long-term open-label Class IV studies (**Level U**). Results of these studies are summarized in this practice guideline but cannot support formal recommendations.

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For patients or clinicians wanting to use nonpharmacologic approaches to treat RLS:

Moderate Evidence	Pneumatic compression, before usual symptom onset (**Level B**).
Weak Evidence	Near-infrared spectroscopy (NIRS) or repetitive transcranial magnetic stimulation (rTMS) (where available) (**Level C**).
	Vibrating pads, for subjective sleep concerns (**Level C**) but not for RLS symptoms **(Level C against**).
	Transcranial direct current stimulation (tDCS), for RLS symptoms (**Level C against**).
Insufficient Evidence	Acupuncture, in RLS (**Level U**).

In patients with secondary RLS associated with end-stage renal disease/hemodialysis (ESRD/HD):

Moderate Evidence	Vitamin C and E supplementation (alone or in combination) (**Level B**).
Weak Evidence	Ropinirole, levodopa, or exercise (**Level C**).
Insufficient Evidence	Gabapentin or IV iron dextran in RLS associated with ESRD/HD (**Level U**). There is also insufficient evidence to support or refute the use of gabapentin or levodopa preferentially over the other in this population (**Level U**).

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Clinical Context

When addressing RLS, clinicians and patients must first determine whether symptoms require treatment, the setting in which this practice guideline is relevant. Treatment should be considered if RLS symptoms interfere with sleep or daytime function to an important degree. Before determining the best treatment, it is important to first ensure there are no contributing factors to RLS symptoms (e.g., iron deficiency or serotonergic antidepressants). Because iron deficiency is a known contributor to RLS, can result in other complications, and may respond to iron supplementation, it is reasonable for clinicians to check iron studies in patients with RLS with new or worsening symptoms and treat the iron deficiency first if indicated.

There are important limitations in the evidence regarding RLS treatments. The clinical significance of some outcomes used in RLS trials, such as PLMI, is uncertain; thus conclusions drawn regarding these outcomes are of unknown clinical relevance. Additionally, apart from the International Restless Legs Syndrome Study Group rating scale (IRLS), clinically important differences for the measures used in RLS trials are unknown, forcing clinicians to use clinical judgment in interpreting study results using these measures/outcomes. Most of the studies are short-term treatment trials, often 12 or fewer weeks, whereas clinical treatment of RLS is ongoing over years. Conclusions regarding long-term efficacy and risks are difficult to develop because of the open-label nature of many of the longer duration studies. Short-term trials are less able to inform risks associated with prolonged medication exposure, such as augmentation occurring with dopaminergic medications. Augmentation is a major concern for clinicians and patients with RLS and an important consideration when choosing a treatment approach. Long-term risks with other treatment approaches, such as opioid use, are also important to consider.

The US Food and Drug Administration dosing guidelines are presented in table e-1 of the published guideline. Most treatments have been investigated only for daily use, and the value of PRN medications for those with intermittent or situation-specific symptoms is unknown, though a substantial number of patients have RLS symptoms on an intermittent basis and may thus need treatment only intermittently.[e2] Additionally, there are no data to guide the approach to cases where monotherapy is not adequately effective or clinicians want to use multiple agents to minimize doses of dopaminergic agents, though one study found that more than 50% of patients in the community are treated with polypharmacy for their RLS.[e104] Clinical trials of RLS medications generally exclude patients with common comorbid conditions such as mood and anxiety disorders and peripheral neuropathy, so the generalizability of these studies to populations with those disorders is uncertain.[e105] Certain populations with secondary RLS, such as pregnant women, are also understudied. In the circumstance where treatment of secondary RLS has the most evidence—patients with ESRD on HD—the presence of evidence specific to this population does not preclude consideration of agents shown helpful for idiopathic RLS but that are to date unstudied in ESRD.

In patients with RLS symptoms requiring treatment, choosing the most appropriate intervention requires an individualized approach including regard for patient factors, such as the most prominent symptoms (e.g., presence of sleep disturbance, because of varying strength of evidence by outcome), comorbidities relating to RLS (e.g., mood), other comorbidities (such that an agent may be used preferentially to treat more than one indication or avoided because of a presumed higher risk of side effects), age (as this could change side effect risks), side effect profile, augmentation risks, and patient preferences (e.g., pharmacologic or nonpharmacologic approaches). Although this practice guideline describes the [adverse effects] commonly reported in the treatment trials—in addition to the risk of augmentation for dopaminergic agents—it is now recognized that some agents for RLS have less common but important risks. These risks include not only cardiac valvulopathy with cabergoline, as discussed earlier, but also side effects such as impulse control disorders with the dopamine agonists. RLS is a chronic condition for many patients. Thus, the relative risks and benefits of long-term medication use are relevant—particularly the appearance of augmentation with the use of dopaminergic agents. Unfortunately, there are insufficient data to guide clinicians in the decision-making process,[e106] as only a few standardized, adjudicated studies of augmentation exist, and the longest comparative or blinded study is only one year in length. Nevertheless, for patients on dopaminergic agents, careful reassessment of changes in the time of RLS symptom onset and its anatomical distribution, total medication dose, and medication timing are indicated at least yearly. In the absence of evidence, it is reasonable to consider discontinuing a patient's current dopaminergic medication in the setting of clinically important augmentation and switching to a nondopaminergic agent or a longer-acting dopaminergic medication.

References

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