Effective Health Care Program

Brain and Nerve Conditions
Restless Legs Syndrome

Treatment for Restless Legs Syndrome

Research Focus for Clinicians

In response to a request from the public, a review was undertaken to evaluate the evidence regarding the potential benefits and adverse effects associated with various treatments for restless legs syndrome (RLS). This review did not cover other sleep disorders such as periodic limb movement disorder. The systematic review included 53 reports of randomized clinical trials and observational studies published through June 2012. The online version of this summary and the full report are available at *www.effectivehealthcare.ahrq.gov/restless-legs.cfm*. This summary is provided to inform discussions with patients of options and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

RLS[†] is a neurological disorder characterized by unpleasant sensations in the legs and an irresistible urge to move them. The essential diagnostic criteria for RLS were established by the International RLS (IRLS) Study Group. Any RLS diagnosis requires that all four of these essential criteria be met:

1. An urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs
2. Unpleasant sensations or the urge to move begin or worsen during periods of rest or inactivity such as lying or sitting
3. Unpleasant sensations or the urge to move are partly or totally relieved by movement such as walking, bending, stretching, et cetera, at least as long as the activity continues
4. Unpleasant sensations or the urge to move are worse in the evening or at night than during the day, or only occur in the evening or night

RLS varies in symptom severity[‡] and frequency. Mild RLS may cause minor annoyance, but severe RLS can negatively affect work, social activities, and function. RLS-induced sleep deprivation and daytime fatigue are common reasons RLS patients seek treatment. Severe RLS can be a chronic progressive disorder that may require long-term treatment.

Prevalence estimates for RLS in the United States range from 1.5 to 7.4 percent in adults. The variation reflects different approaches to diagnosing RLS and defining its frequency and severity. The etiology of primary RLS is unknown, but the disorder might occur secondary to other conditions such as iron deficiency, end-stage renal disease, and pregnancy. Insufficient sleep and sleep disorders such as sleep apnea might exacerbate symptoms of RLS.

Treatment options for RLS include nonpharmacologic and pharmacologic strategies. Nonpharmacologic treatment approaches include pneumatic compression devices, near-infrared light therapy, lower body resistance exercise, and using botanical preparations. The major classes of pharmacologic agents used are listed in Table 1. The choice of pharmacologic agent used to treat RLS depends on the frequency and severity of symptoms.

Dopaminergic agents can result in a treatment complication called augmentation. Augmentation is a drug-induced exacerbation of symptoms characterized by greater symptom intensity, onset earlier in the day, and shorter latency during inactivity. With augmentation, symptoms may also spread to the arms, trunk, and face. Recent studies suggest augmentation is more likely to occur with levodopa when compared with dopamine agonists. Augmentation can lead to poorer outcomes, a switch to other classes of medication, or treatment discontinuation.[1,2] Augmentation is usually considered as resolved when the medication triggering augmentation has been discontinued or when the patient has been switched to another medication.[1,2]

Clinicians face uncertainty related to defining RLS, assessing disease severity, and evaluating the risks and benefits of treatment. While these challenges apply to both primary care and specialty settings, they may be more pronounced in primary care.

[†] Also referred to as Willis-Ekbom disease

[‡] RLS can be defined as mild, moderate, severe, or very severe based on the IRLS Rating Scale. The IRLS is a 10-item scale with scores ranging from 0 (no symptoms) to 40. Scores ≤10 are considered as mild, scores 11–20 as moderate, scores 21–30 as severe, and scores >30 as very severe RLS.

1. Garcia-Borreguero D, Hogl B, Ferini-Strambi L, et al. Mov Disord. 2012;27(2):277-83. PMID: 22328464.
2. Allen RP, Adler CH, Du W, et al. Sleep Med. 2011;12(5):431-9. PMID: 21978726.

Table 1. Pharmacologic Interventions Assessed in This Comparative Effectiveness Review*

Treatment	Generic Name	FDA Approval for RLS	Brand Name
Dopaminergic agents	Levodopa	No	Dopar®
	Ropinirole	Yes	Requip®
	Pramipexole	Yes	Mirapex®
	Rotigotine patch	Yes	Neupro®
Anticonvulsants (alpha-2-delta ligands)	Gabapentin enacarbil	Yes	Horizant®
	Gabapentin	No	Neurontin®
	Pregabalin	No	Lyrica®
Iron	Many formulations	No	-

* Sedative hypnotics and opioids were included in this review; however, no eligible studies assessed these agents in patients with RLS. Sedative hypnotics and opioids have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of RLS.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Conclusion

When compared with placebo, dopamine agonists and alpha-2-delta ligands reduce RLS symptoms and improve patient-reported sleep outcomes and disease-specific quality of life. Moderate-level evidence suggests benefits of intravenous iron on symptoms of RLS. No eligible studies assessed opioids or sedative hypnotics as treatment for RLS. These agents also have potentially serious adverse effects. Some nonpharmacologic interventions such as compression stockings, near-infrared light, or exercise improve RLS symptoms (evidence level low to moderate). Adverse effects of pharmacologic therapies and long-term treatment withdrawals due to adverse effects or lack of efficacy are common. Evidence from observational studies suggests that augmentation is common across dopaminergic agents. The studies included in this review were conducted in adults with moderate to severe RLS. The long-term effectiveness and applicability of the assessed RLS therapies for adults with milder or less frequent RLS symptoms, individuals with secondary RLS, and children are unknown.

Clinical Bottom Line

Rating Scales Used To Evaluate Patient Outcomes

The International RLS (IRLS) Rating Scale is a 10-item scale where items such as intensity, frequency, and consequences of RLS are rated by patient and investigator on a 5-point scale to give a global score ranging from 0 (no RLS) to 40 (very severe RLS). Clinically meaningful responder criteria are the resolution of symptoms (score = 0); the percentage of patients with reduction of symptoms from very severe or severe to moderate or mild; and a 50-percent or greater change in the score from baseline.

The Clinical Global Impressions (CGI) or **Patient Global Impressions (PGI) Scale** has individual items such as disease severity, improvement from baseline, therapeutic effect, and side effects from treatment. Items are rated on a 7-point scale. Scores are not combined; often just one component of the scale (e.g., improvement) is assessed by the clinician (CGI) or the patient. Clinically meaningful responder criteria are the percentages of patients who are much improved or very much improved on the CGI Scale or the PGI Scale.

The RSL Quality of Life (RLS-QoL) Scale is an 18-item scale where items such as daily function, social activities and travel arrangements, morning activities and concentration, and sleep and sexual activity are rated on a 5-point scale to give a global score.

The Medical Outcomes Study-Sleep Problem Index II (MOS-SPI-II) Scale is a 12-item scale where several aspects of sleep such as sleep initiation, maintenance, quantity, quality, sleep adequacy, and daytime somnolence are rated by the patient.

Evidence of Benefits

Dopamine agonists (ropinirole, pramipexole, and rotigotine)

When compared with placebo, dopamine agonists:
- Increased the percentage of patients with a clinically important response* ●●●
- Reduced RLS symptoms ●●●
- Improved RLS quality of life ●●●
- Improved patient-reported sleep outcomes ●●●

Alpha-2-delta ligands (gabapentin enacarbil and pregabalin)

When compared with placebo, alpha-2-delta ligands:
- Increased the percentage of patients with a clinically important response* ●●●
- Improved RLS quality of life ●○○
- Improved patient-reported sleep outcomes ●○○

Gabapentin enacarbil also improved sleep adequacy based on the sleep adequacy domain of the MOS-SPI-II Scale. ●●●

Iron therapy

Results from one small, good-quality study† showed that, when compared with placebo, intravenous ferric carboxymaltose:
- Slightly improved symptom scores on the IRLS Rating Scale ●●○
- Slightly improved RLS quality of life ●●○
- Slightly improved patient-reported sleep outcomes ●○○

Two small randomized trials of iron therapy (one intravenous and one oral) versus placebo in adults with iron deficiency suggested that iron may improve both the percentage of adults considered IRLS responders and symptom scores on the IRLS Rating Scale.** ●○○

(Continued in the next column)

Evidence of Benefits *(Continued)*

Opioids and hypnotics

No eligible studies assessed opioids or sedative hypnotics, though these are sometimes used clinically for RLS treatment. ○○○

Nonpharmacologic interventions

Pneumatic compression devices reduced IRLS Rating Scale symptom scores more than sham. ●●○

Near-infrared light treatment improved IRLS Rating Scale symptom, scores more than sham. ●○○

Strength training and treadmill walking improved IRLS symptoms but adherence was poor. ●○○

The botanical extract valerian was not effective in treating RLS. ●○○

(Continued with footnotes on the next page)

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence is either unavailable or does not permit a conclusion.

Clinical Bottom Line *(Continued)*

Evidence of Harms

Dopamine agonists (ropinirole, pramipexole, and rotigotine)

Dopamine agonists were associated with more adverse effects than placebo.

- Study withdrawals due to adverse effects were more common with dopamine agonists than with placebo. The differences were mainly due to adverse effect-related withdrawals reported in studies of transdermal rotigotine. ●●○
- More patients randomized to a dopamine agonist had at least one adverse effect when compared with placebo. ●●●
- Short-term adverse effects from dopamine agonist treatment included nausea, vomiting, somnolence, and fatigue. ●●●

Evidence from observational studies suggests that augmentation is common across dopaminergic agents (dopamine agonists and levodopa), with prevalence estimates ranging from 2.3 to 60 percent. The reason for the wide variation in prevalence estimates across drugs is unclear. ††

(Continued in the next column)

Evidence of Harms *(Continued)*

Alpha-2-delta ligands (gabapentin enacarbil and pregabalin)

Alpha-2-delta ligands were associated with more adverse effects than placebo.

- More patients randomized to alpha-2-delta ligands had at least one adverse effect when compared with placebo. ●●○
- Somnolence, unsteadiness or dizziness, and dry mouth were much more common with alpha-2-delta ligands than with placebo. ●●●
- Study withdrawals (due to any reason) were less common with alpha-2-delta ligands than with placebo. ●●●

* These are patients with a greater than 50-percent reduction in symptom scores on the IRLS Rating Scale or who were "improved" or "much improved" on the CGI Scale or the PGI Scale.

† Serum ferritin levels were 26.8 mcg/L for females and 63.6 mcg/L for males among patients included in this trial.

** In the trial evaluating intravenous iron, serum ferritin levels were reported to be 20.55 mcg/L in the included patients. Serum ferritin levels were not reported in the trial evaluating oral iron therapy.

†† This finding was not rated.

Table 2. Individual Outcomes and Strength of Evidence in Placebo-Controlled Studies of Dopamine Agonists

Outcome for Treatment vs. Placebo, Strength of Evidence	RLS Treatment That Was Compared With Placebo	Number of Trials	n	Summary Statistics [95% CI] for Comparisons of RLS Treatment vs. Placebo	Absolute Effect per 100 Patients [95% CI]
Increase in IRLS Rating Scale responders (>50% score reduction) ●●●	Pramipexole	3	1,079	RR 1.46 [1.22 to 1.74]	21 more per 100 [10 to 34 more]
	Rotigotine	4	1,139	RR 1.76 [1.47 to 2.10]	25 more per 100 [16 to 37 more]
Increase in Clinical Global Impressions Scale responders (very or much improved) ●●●	Pramipexole	5	1,747	RR 1.61 [1.40 to 1.86]	25 more per 100 [17 to 36 more]
	Ropinirole	6	1,608	RR 1.37 [1.25 to 1.50]	18 more per 100 [12 to 24 more]
	Rotigotine	4	1,091	RR 1.37 [1.22 to 1.54]	19 more per 100 [12 to 28 more]
Improvement in RLS quality of life ●●●	Pramipexole	3	912	SMD -0.43 [-0.61 to -0.25]	Not reported
	Ropinirole	2	643	SMD -0.30 [-0.45 to -0.14]	Not reported
	Rotigotine	4	585	SMD -0.37 [-0.60 to -0.13]	Not reported
Improvement in patient self-rated sleep using the MOS-SPI-II Scale ●●●	Pramipexole	1	356	SMD 0.36 [0.15 to 0.57]	Not reported
	Ropinirole	4	1,237	SMD 0.37 [0.24 to 0.49]	Not reported
	Rotigotine	3	459	SMD 0.43 [0.24 to 0.61]	Not reported
Increase in study withdrawals due to an adverse event ●●○	Pramipexole	5	1,791	RR 0.97 [0.69 to 1.35]	Not reported
	Ropinirole	7	1,698	RR 1.48 [0.99 to 2.20]	Not reported
	Rotigotine	4	1,370	RR 2.50 [1.33 to 4.70]	Not reported
Increase in number of patients with >1 adverse event ●●●	Pramipexole	5	1,790	RR 1.16 [1.04 to 1.29]†	Not reported
	Ropinirole	7	1,695	RR 1.20 [1.10 to 1.32]	Not reported
	Rotigotine	4	1,369	RR 1.25 [1.00 to 1.59]	Not reported

Abbreviations: 95% CI = 95-percent confidence interval; IRLS = International Restless Legs Syndrome; MOS-SPI-II = Medical Outcomes Study Sleep Problem Index II; RR = relative risk; SMD = standardized mean difference

Relative Risk: A comparison of the risk of a particular event for two different groups of people, one of which may be treated with a drug and the other with a control.

Standardized Mean Difference: A way of standardizing the "intervention effect" [the difference between treatment and control group means] that allows for making comparisons across studies.

† As an example, an RR of 1.16 implies that patients on pramipexole have a 16-percent higher chance of having >1 adverse event when compared with patients on placebo.

Table 3. Individual Outcomes and Strength of Evidence in Placebo-Controlled Studies of Alpha-2-Delta Ligands

Outcome for Treatment vs. Placebo, Strength of Evidence	RLS Treatment That Was Compared With Placebo	Number of Trials	n	Summary Statistics [95% CI] for Comparisons of RLS Treatment vs. Placebo	Absolute Effect per 100 Patients [95% CI]
Increase in IRLS Rating Scale responders (>50% score reduction) ●●●	Gabapentin enacarbil	1	321	RR 1.54 [1.18 to 2.01]	21 more per 100 [7 to 40 more]
	Pregabalin	2	182	RR 2.03 [1.33 to 3.11]	34 more per 100 [11 to 69 more]
Increase in Clinical Global Impressions Scale responders (much or very much improved) ●●●	Gabapentin enacarbil	2	431	RR 1.80 [1.51 to 2.14]	33 more per 100 [21 to 48 more]
	Pregabalin	1	44	RR 1.14 [0.80 to 1.64]	9 more per 100 [12 fewer to 40 more]
Improvement in RLS quality of life ●○○	Gabapentin enacarbil	1	538	SMD 0.42 [0.16 to 0.69]	Not reported
	Pregabalin	1	124	SMD -0.05 [-0.65 to 0.55]	Not reported
Improvement in patient self-rated sleep using the MOS-SPI-II Scale ●●●	Gabapentin enacarbil	2	431	SMD 0.53 [0.33 to 0.72]	Not reported
Increase in number of patients with >1 adverse event ●●○	Gabapentin enacarbil	3	738	RR 1.09 [1.00 to 1.19]	Not reported
	Pregabalin	2	195	RR 1.67 [0.74 to 3.80]	Not reported

See the legend under Table 2.

Gaps in Knowledge

- Most studies included in this review were efficacy studies. No studies making head-to-head comparison between RLS medications were identified. The included studies did not permit reliable conclusions about comparative benefits and harms.
- The current evidence base consists almost exclusively of pharmacologic treatments. The effectiveness of nonpharmacologic treatments including herbal therapy, mind-body medicine, and manipulative treatments is not known. Additionally, the effectiveness of over-the-counter iron supplements is not known.
- Most of the studies included in this review were conducted in patients with moderate to severe RLS. The effectiveness of the assessed treatments in patients with mild RLS is unknown.
- No evidence was found about the effectiveness of therapies in specific subgroups such as children, older adults with multiple comorbidities, or individuals with secondary RLS (including those with iron deficiency or end-stage renal disease and pregnant women).
- The long-term durability of treatment benefits remains unknown.
- Little is known about patient characteristics that may lead to augmentation.
- The included studies do not consistently report on the use of objective criteria for sleep assessment.
- There is a paucity of information on the effects of environmental factors on RLS and their impact on treatment outcomes.

Resource for Patients

Options for Treating Restless Legs Syndrome, A Review of the Research for Adults, is a free companion to this clinician research summary. It can help patients talk with their health care professionals about the many options for treating RLS.

What To Discuss With Your Patients and Their Caregivers

- What RLS is, and that it is a treatable condition
- That RLS can become a chronic condition that requires treatment in moderate to severe cases
- The currently available pharmacologic and nonpharmacologic therapies for RLS
- The available evidence for the effectiveness of the various treatments for RLS with regard to disease symptoms, quality of life, and sleep outcomes
- The available evidence for the harms of the various treatments for RLS
- The possibility that the patient might develop augmentation if he/she is taking levodopa or dopamine agonists
  - Ask the patient at each visit if he/she is experiencing symptoms of augmentation.

Ordering Information

For electronic copies of *Options for Treating Restless Legs Syndrome, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/restless-legs.cfm*. To order free print copies of this clinician research summary, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

The information in this summary is based on *Treatment for Restless Legs Syndrome*, Comparative Effectiveness Review No. 86, prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I for the Agency for Healthcare Research and Quality, November 2012. Available at *www.effectivehealthcare.ahrq.gov/restless-legs.cfm*. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

AHRQ Pub. No. 12(13)-EHC147-3
August 2013