Annals of Internal Medicine®

In the Clinic®

Restless Legs Syndrome

Restless legs syndrome (RLS), or Willis-Ekbom disease, is a common sensorimotor neurologic disorder characterized by an urge to move the legs that often is associated with discomfort or dysesthesia.

Diagnosis

Treatment

Practice Improvement

Tool Kit

Patient Information

The CME quiz is available at www.annals.org/intheclinic.aspx. Complete the quiz to earn up to 1.5 CME credits.

Physician Writer
Suzanne Bertisch

CME Objective: To review current evidence for diagnosis, treatment, and practice improvement for restless legs syndrome.

Funding Source: American College of Physicians.

Disclosures: Dr. Bertisch, ACP Contributing Author, reports grants from UCB Pharmaceuticals and Merck outside the submitted work. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-1891.

With the assistance of additional physician writers, the editors of ***Annals of Internal Medicine*** develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians.

In the Clinic does not necessarily represent official ACP clinical policy. For ACP clinical guidelines, please go to https://www.acponline.org/clinical_information/guidelines/.

Acknowledgment: The author thanks Julia S. Whelan, MS, AHIP, Harvard Medical School, who provided valuable assistance with conduct of the complex systematic review; and John W. Winkelman, MD, PhD, Massachusetts General Hospital, Harvard Medical School, and Catherine Buettner, MD, MPH, Beth Israel Deaconess Medical Center, Harvard Medical School, who provided invaluable comments and suggestions on a draft of the manuscript.

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

The prevalence of RLS ranges from about 2%–4% in adults in the general population (1, 2). Given the timing of onset and the association with immobility, patients commonly report sleep disturbance in addition to sensory symptoms. RLS varies in severity, with some patients experiencing mild, infrequent symptoms and other patients having severe, daily symptoms that cause substantial sleep disturbance and reduce quality of life.

The REST general population study of more than 16 000 adults, done in 5 European countries and the United States, reported that the rate of RLS in women is about twice that of men across all age groups (1).

RLS is more common in patients with chronic kidney disease, iron deficiency anemia, pregnancy, and chronic neurologic disorders and is exacerbated by some drugs. Nonpharmacologic treatment focuses on correcting contributing factors, such as low-normal iron stores or removal of offending medications, as well as distraction strategies. However, these recommendations are informed mainly from clinical experience rather than empirical data. In patients with moderate–severe RLS, the clinical efficacy of dopamine agonists, and more recently alpha-2 delta ligands (e.g., gabapentin enacarbil or pregabalin) has been established.

Diagnosis

What is RLS?

Although RLS is classified as a sleep disorder, its essential diagnostic criteria (see the **Box**) (3), developed from an expert consensus process (3, 4), are defined by patient-reported symptoms and patterns experienced during relaxed wakefulness. The abnormal sensations that often occur along with the urge to move are described as creepy-crawly, electrical, jittery, burning, or a need to stretch and are often described as "inside of the leg" (5). The urge to move can also involve other parts of the body, such as the arms.

Supportive features include a family history of RLS, periodic limb movements of sleep, and improvement of symptoms with dopaminergic agents (6). Patients and their bed partners often mistake leg kicking or movements at night to be RLS. Periodic limb movements of sleep are defined as involuntary, repetitive movements 0.5–10.0 seconds in duration that generally involve dorsiflexion of the first metatarsal with partial flexion of the ankle, knee, or hip and occur during sleep (7). They are present in >80% of patients with RLS but are also common in persons with other sleep disorders as well as in healthy sleepers.

What symptoms should prompt clinicians to consider RLS?

All patients presenting with insomnia should be asked about the presence of RLS symptoms, because more than 88% of patients with RLS report at least 1 sleep symptom (inability to fall asleep, inability to stay asleep, or poor-quality sleep) in addition to an uncontrollable urge to move the legs or dysesthesia. Other patient-reported symptoms commonly attributed to RLS include leg pain, fatigue, leg jerks, and daytime sleepiness (1, 8, 9).

What physical examination findings indicate possible RLS?

No physical findings are associated with idiopathic RLS, but a physical examination may reveal findings related to an associated condition when RLS is present with low systemic iron stores, pregnancy, renal disease, diabetes, or neuropathy.

1. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16:283-95. [PMID: 21795081]
2. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005; 165:1286-92. [PMID: 15956009]
3. International Restless Legs Syndrome Study Group. 2012. Accessed at http://irlssg.org/diagnostic-criteria/ on 3 August 2014.
4. Allen RP, Picchietti DL, Garcia-Borreguero D, et al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014; 15:860-73. [PMID: 25023924]
5. Garcia-Borreguero D, Stillman P, Benes H, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol. 2011;11:28. [PMID: 21352569]
6. Allen RP, Picchietti D, Hening WA, et al; Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4:101-19. [PMID: 14592341]
7. Aurora RN, Kristo DA, Bista SR, et al; American Academy of Sleep Medicine. The treatment of restless legs syndrome and periodic limb movement disorder in adults–an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012;35:1039-62. [PMID: 22851801]

Diagnostic Criteria for Restless Legs Syndrome From the International Restless Legs Syndrome Study Group*

All criteria must be met.

1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, an uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

*Diagnostic criteria; 2012. Accessed at http://irlssg.org/diagnostic-criteria/ on 3 August 2014.

What other evaluations should be performed in patients suspected of having RLS?

The evaluation of RLS involves review of the essential diagnostic criteria, a careful history of the timing and onset of symptoms, supporting features, potential "mimics", and exacerbating factors. Key elements of assessment include the *timing* and severity of RLS symptoms, effect on daytime mood and function, medical history, symptoms of other sleep disorders, family history, and medications. RLS severity can be quantified in the clinical setting using the International Restless Legs Syndrome (IRLS) Study Group Rating Scale (10) in the sleep laboratory with the suggested immobilization test (11, 12) and with objective quantification of associated periodic leg movements using an accelerometer (13). However, accelerometers are generally reserved for the research setting and their clinical utility is unclear (13). Many drugs and medications have been implicated in exacerbating RLS, but recommendations are not always supported by empirical data. Numerous serotonergic antidepressants have been documented to exacerbate RLS in prospective studies (14), and clinical consensus recommends avoiding other classes of medications, such as dopamine-blocking antiemetics, centrally acting antihistamines, antipsychotics, alcohol, and caffeine. Associated conditions, such as low systemic iron stores, pregnancy, renal disease, diabetes, or neuropathy, should also be considered. Common mimics include leg cramps, neuropathy, arthritis, peripheral vascular disease, and akathisia and can generally be differentiated from RLS during clinical evaluation (**Table 1**). Iron studies are recommended, even in the absence of anemia (15). RLS is a clinical diagnosis, and sleep testing (e.g., polysomnography) or other objective studies (e.g., nerve conduction studies) are not routinely indicated, unless concern for another disorder (e.g., obstructive sleep apnea) exists (16). Referral to a sleep specialist or neurologist is not needed to confirm the diagnosis but may be warranted in the presence of an uncertain diagnosis or coexisting sleep disorder, neurologic disorder, or other complex medical condition.

8. Hening W, Walters AS, Allen RP, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med. 2004;5:237-46. [PMID: 15165529]
9. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med. 2006; 7:545-52. [PMID: 16740407]
10. Walters AS, LeBrocq C, Dhar A, et al; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med. 2003;4:121-32. [PMID: 14592342]
11. Montplaisir J, Boucher S, Nicolas A, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. Mov Disord. 1998;13:324-9. [PMID: 9539348]
12. Michaud M, Lavigne G, Desautels A, Poirier G, Montplaisir J. Effects of immobility on sensory and motor symptoms of restless legs syndrome. Mov Disord. 2002;17: 112-5. [PMID: 11835447]
13. Plante DT. Leg actigraphy to quantify periodic limb movements of sleep: a systematic review and meta-analysis. Sleep Med Rev. 2014;18:425-34.
14. Hoque R, Chesson AL Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med. 2010;6:79-83. [PMID: 20191944]
15. Mackie S, Winkelman JW. Normal ferritin in a patient with iron deficiency and RLS. J Clin Sleep Med. 2013;9: 511-3. [PMID: 23674944]
16. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28:499-521. [PMID: 16171294]

Table 1. **Diagnostic Mimics of Restless Legs Syndrome***

Symptom	*Number of Criteria†*	*Distinguishing Factors*	*Coexists With Restless Legs Syndrome*
Leg cramps	4 of 4	Muscle spasm easily identified	+
Neuropathy	1 of 4	Numbness, burning, tingling, *without* an urge to move	+++
Arthritis	2-3 of 4	Discomfort in joints at rest; improves with movement	++
Vascular	2-3 of 4	Varied: Worse with walking; +/− relief with movement; varicosities and signs of peripheral vascular disease on examination	++
Positional discomfort	1-2 of 4	Foot or leg "asleep" from compression; resolves with shifting	–
Akathisia	4 of 4	Urge to move, all over, caused by dopamine antagonists	+

** Courtesy of J.W. Winkelman, MD, PhD.*
† The 4 criteria listed refer to the first 4 diagnostic criteria listed in the ***Box*** *(Diagnostic Criteria for Restless Legs Syndrome From the International Restless Legs Syndrome Study Group). The fifth criterion in the box is the need to rule out mimics.*

Diagnosis... The diagnosis of RLS is based on the presence of clinical diagnostic criteria. Timing, frequency, and severity of symptoms are key components of the history. RLS can usually be distinguished from mimics based on history and physical examination. Consider the possibility of associated conditions, such as iron deficiency. Polysomnography or other diagnostic studies are generally not indicated, unless there is a concern for a comorbid sleep disorder, neurologic condition, or complex medical condition.

CLINICAL BOTTOM LINE

Treatment

What nondrug therapies should clinicians recommend for RLS?

The goals of RLS treatment are to reduce symptoms as well as the distress and anxiety of sleep disturbance and to improve daytime function. Nonpharmacologic strategies largely focus on distracting activities and avoidance of RLS triggers and are based on clinical experience. Avoidance of drugs that might provoke RLS is recommended, although potential offending medications (e.g., antidepressants) should be withdrawn only after considering the patient's overall status and in consultation with other health providers. Mental-alerting strategies, such as knitting and video games, as well as activities that require standing, locomotion, or movement, such as ironing, massage, or stretching, can help prevent or alleviate RLS symptoms. Small trials have observed improvement of RLS symptoms with pneumatic compression devices (17) and near-infrared light treatment (18), although larger studies are needed before these therapies can be routinely recommended. Small studies have also demonstrated that aerobic training, resistance training (19), and intradialytic exercise (20, 21) improve RLS symptoms, although some patients do report exacerbations after exercise. Sleep deprivation worsens RLS (22, 23), so adequate duration and quality of sleep are recommended.

*A 2012 Cochrane meta-analysis that included 4 clinical trials (*n *= 139 patients) concluded that evidence of efficacy for treating RLS with iron was insufficient (24), and guidelines from the American Academy of Sleep Medicine (AASM) (7) and the IRLS Study Group (25) have concluded that there is very low or insufficient*

17. Lettieri CJ, Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. Chest. 2009;135:74-80. [PMID: 19017878]
18. Mitchell UH, Myrer JW, Johnson AW, Hilton SC. Restless legs syndrome and near-infrared light: An alternative treatment option. Physiother Theory Pract. 2011;27:345-51. [PMID: 20977377]
19. Aukerman MM, Aukerman D, Bayard M, et al. Exercise and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med. 2006;19:487-93. [PMID: 16951298]
20. Mortazavi M, Vahdatpour B, Ghasempour A, et al. Aerobic exercise improves signs of restless leg syndrome in end stage renal disease patients suffering chronic hemodialysis. ScientificWorldJournal. 2013;2013:628142. [PMID: 24307876]
21. Giannaki CD, Sakkas GK, Karatzaferi C, et al. Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. BMC Nephrol. 2013;14:194. [PMID: 24024727]
22. Trenkwalder C, Hening WA, Walters AS, et al. Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. Mov Disord. 1999;14:102-10. [PMID: 9918351]

evidence to treat RLS with iron. Yet, expert consensus guidelines suggest that iron therapy should be attempted in patients whose serum ferritin levels are in the low-normal range (<45–75 μg/L) (26–28).

The oral daily dose of elemental iron in adults is 150–200 mg/day, and the cause of low iron stores should be assessed. Oral ferrous salts should be used, given their greater bioavailability, and patients should be educated about factors that influence absorption, such as the need for coadministration with vitamin C, the advantage of avoiding taking with food, and the disadvantages of enteric-coated formulations. Medications, such as levodopa, levothyroxine, and proton-pump inhibitors, can also impede absorption (29). Given its low cost, ferrous sulfate 325 mg (60 mg elemental iron) 3 times/day with vitamin C is a sufficient starting dose. Gastrointestinal side effects are common, and reducing the dose or changing the formulation to ensure patient adherence may be needed. The optimal dosage of iron supplementation is unclear, although an amount adequate to ensure serum ferritin levels >75 μg/L is recommended (26, 30); persons whose systemic iron stores do not increase should be assessed.

How should clinicians choose and dose drugs?

The decision to initiate pharmacologic therapy should be individualized to achieve the goals of therapy, which are to reduce RLS symptoms, associated sleep disturbance, and functional limitations and to improve quality of life. Patients with mild or intermittent symptoms generally do not require pharmacologic therapy, other than during situations that limit mobility (e.g., air travel). Regular use of pharmacologic therapy should be reserved for patients who experience almost daily or daily moderate or severe symptoms that interfere with sleep or impair daytime functioning (30). Administration of medication is dependent on the timing of and activities associated with RLS symptoms, and timing of treatment is essential to effectiveness. It is important to establish the expectation that the focus of treatment is reducing bothersome symptoms and not on eradication of symptoms.

Expert consensus guideline recommendations for treatment of intermittent RLS include carbidopa/levodopa (25/100 mg), dopamine agonists, benzodiazepines, and low-potency opioids (5, 30). Carbidopa/levodopa was the first drug to be formally investigated for RLS (31), and several small studies have shown that it modestly improves symptoms, improves quality of life, and substantially improves sleep quality compared with placebo (32). However, use has been limited by high rates of rebound symptoms and augmentation (i.e., worsening of symptoms with dopaminergic treatment). Data supporting the use of benzodiazepines or low-potency opioids are limited, and these medications should rarely, if ever, be used, given their known risks and harms.

Pharmacologic agents approved by the U.S. Food and Drug Administration (FDA) for moderate-to-severe RLS (IRLS severity score ≥15) include dopamine agonists (pramipexole, ropinirole, rotigotine) and alpha-2 delta ligands (gabapentin enacarbil). Physicians also prescribe a number of drugs without an FDA indication for RLS, including other alpha-2 delta ligands (gabapentin, pregabalin) and opioids. There are no FDA-approved drugs for RLS that have been found safe and effective in pregnancy. Most studies investigating pharmacologic therapies have been of short duration (i.e., ≤12 weeks); limited to participants with moderate–severe RLS (IRLS score ≥15) of generally long duration, many of whom had previously been treated; and consisted of >90% white participants, which limits

23. Hening WA, Walters AS, Wagner M, et al. Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. Sleep. 1999;22:901-12. [PMID: 10566908]
24. Trotti LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. Cochrane Database Syst Rev. 2012;5:CD007834. [PMID: 22592724]
25. Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med. 2013;14:675-84. [PMID: 23859128]
26. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. Sleep Med. 2009;10:973-5. [PMID: 19230757]
27. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994;23:200-3. [PMID: 8085504]
28. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep. 1998;21:371-7. [PMID: 9646381]
29. National Institutes of Health, Office of Dietary Supplements. Iron dietary supplement fact sheet; 2014.
30. Silber MH, Becker PM, Earley C, et al; Medical Advisory Board of the Willis-Ekbom Disease Foundation. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. Mayo Clin Proc. 2013;88:977-86. [PMID: 24001490]
31. von Scheele C. Levodopa in restless legs. Lancet. Lancet. 1986;2:426-7.
32. Scholz H, Trenkwalder C, Kohnen R, et al. Levodopa for restless legs syndrome. Cochrane Database Syst Rev. 2011:CD005504. [PMID: 21328278]

Table 2. **Use of Dopamine Agonists and Alpha-2 Delta Ligands for Treatment of Restless Legs Syndrome***

Variable	*Dopamine Agonists*			*Alpha-2 Delta Ligands*		
	Pramipexole†	*Ropinirole†*	*Rotigotine Transdermal†‡*	*Gabapentin Enacarbil†*	*Gabapentin*	*Pregabalin*
Time of maximum concentration, *h*	2	1–2	15–18	5–7	1	3–4
Half-life, *h*	8	6	5–7	5–6	5–7	6
Initial dose, *mg*	0.125	0.5 (0.25)	1mg/24h	600	300	100
Usual dose, *mg*	0.125–0.5	0.5–2.0	1.0–3.0	600	300–1800, divided	100–300
Max dose, *mg*	(0.75–1.0)	4.0	3.0	600 (1200)	3600	450
Metabolism	Renal	Hepatic	Hepatic	Intestinal/renal	Renal	Renal
Common side effects	Nausea, vomiting, fatigue, somnolence, augmentation, application site reactions (rotigotine)			Somnolence, unsteadiness/dizziness, weight gain, dry mouth		

FDA = U.S. Food and Drug Administration.
** FDA-approved prescribing information and sources. Published pharmacokinetic data are not consistently reported for all drugs. Data in parentheses are non-FDA approved doses observed in published data or clinical observation for FDA-approved drugs. Adapted from reference 30.*
† FDA approved for moderate-to-severe primary restless legs syndrome.
‡ Delivered continuously, for 24 hours after application to skin.

the generalizability of the results for clinical practice (33). Only a few trials evaluated longer-term efficacy (6-52 months) (34–36), and dropout rates were commonly about 20%. There have been very few comparative effectiveness studies to guide determination of "first-line" therapy (36).

Dopamine agonists

Dopaminergic agents have been used to treat RLS since a report in 1982 noted improvement in 5 patients receiving levodopa. Recommended agents include pramipexole, ropinirole, and rotigotine. Ergot derivatives, such as cabergoline, are no longer recommended because of the risk for cardiac valve disease (37, 38) and extracardiac fibrosis. Recommended drugs share a common mechanism of action, with differences in their affinity for dopamine receptors and pharmacokinetics (**Table 2**). More than 35 trials have evaluated their efficacy (39).

*Several recent meta-analyses of clinical trials (33, 39–41) have shown short-term efficacy of dopamine agonists in reducing RLS symptoms as measured by the IRLS Study Group Rating Scale and Clinical Global Impression (CGI) Improvement Scale. These studies have also noted significant improvements in frequency of periodic limb movements of sleep, self-reported sleep quality, quality of life, and depressive symptoms (***Table 3***), but not improvement in sleep architecture. Individual dopamine agonists seem to have similar efficacy; however, no head-to-head comparative studies have been done.*

Pramipexole and ropinirole should be taken 1–2 hours before the expected onset of symptoms. The lowest recommended dose should be initiated, with an adequate interval before titration (**Table 2**) (42). If symptoms occur earlier in the day, additional early dosing can be considered. Doses should not exceed 1 mg for pramipexole (maximum FDA-approved dose, 0.5 mg), 4 mg for ropinirole, and 3 mg for rotigotine within a 24-hour period. Higher doses increase risk for augmentation (see below). These dosages are substantially lower than those used for treating Parkinson disease.

The most common side effects include nausea, somnolence, and site application reactions with rotigotine. Rates of orthostatic hypotension with dopamine agonists are lower in patients with

33. Wilt TJ, MacDonald R, Ouellette J, et al. Pharmacologic therapy for primary restless legs syndrome: a systematic review and meta-analysis. JAMA Intern Med. 2013;173:496-505. [PMID: 23460396]
34. Trenkwalder C, Benes H, Poewe W, et al; SP790 Study Group. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2008;7:595-604. [PMID: 18515185]
35. Högl B, Garcia-Borreguero D, Trenkwalder C, et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. Sleep Med. 2011;12:351-60. [PMID: 21354368]
36. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med. 2014; 370:621-31. [PMID: 24521108]
37. Zanettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med. 2007;356:39-46. [PMID: 17202454]
38. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med. 2007;356:29-38. [PMID: 17202453]

Table 3. **Quantitative Reviews of Pharmacologic Treatment of Restless Legs Syndrome 2009–2014***

Study, Year (Reference)	*Description*	*Outcomes, MD or RR (95% CI)*		
		Dopamine Agonists	*Anticonvulsants*	*Iron*
Hornyak, et al, 2014 (39)	62 RCTs of dopamine agonists, anticonvulsants (11/13 studies alpha-2 delta ligands), benzodiazepines, opioids, iron (*n* = 9596)	**IRLS Score**		
		MD, −5.5 (−6.4 to −4.6)	MD, −5.1 (−6.8 to −3.5)	MD, −4.6 (−8.0 to −1.2)
		CGI Responders		
		RR, 1.4 (1.3 to 1.5)	RR, 1.7 (1.5 to 2.0)	–
		PLMI Events/h		
		−22.5 (28.0 to 17.0)	−8.5 (−15.2 to −1.8)	–
		Adverse Events		
		OR, 2.6 (1.5, 5.0)	OR, 2.5 (1.8 to 3.4)	OR, 4.0 (1.3 to 12.1)
Wilt, et al, 2013 (33)	Placebo-controlled studies of dopamine agonists (*n* =16; *N* = 4861), alpha-2 delta ligands (*n* = 7; *N* = 1096)	**IRLS Score**		
		−4.6 (−5.4 to −3.7)	–	–
		CGI Responders		
		68% vs. 46%; RR, 1.4 (1.3 to 1.5)	74% vs. 44%; RR, 1.6 (1.2 to 2.1)	–
		IRLS Responders (≥50% Score Reduction)		
		61% vs. 41%; RR, 1.6 (1.4 to 1.9)	61% vs. 37%; RR, 1.7 (1.33 to 2.09)	–
		Adverse Events		
		RR, 1.2 (1.1 to 1.3)	RR, 1.2 (1.0 to 1.4)	–
Zhang, et al, 2013 (41)	6 studies investigating pramipexole for primary RLS (*n* = 1469)	**IRLS Score**		
		MD, −6.0 (−7.8 to −4.4)	–	–
		IRLS Responders (≥50% Score Reduction)		
		OR, 2.5 (2.0 to 3.2)	–	–
		CGI Responders		
		OR, 3.1 (2.5 to 4.0)	–	–
		PGI Responders		
		OR, 2.8 (1.9 to 4.1)	–	–
		Adverse Events		
		Nausea: RR, 2.7 (1.8, to 4.0); fatigue RR, 1.8 (1.1, 2.9)		
Trotti, et al, 2012 (24)	4 controlled studies of oral or intravenous iron (*n* = 139)	**IRLS Score**		
		–	–	MD, −3.8 (−7.7 to 0.1)
		Adverse Events		
		–	–	RR, 1.4 (0.9 to 2.3)
Zintzaras, et al, 2010 (40)	18 RCTs of dopamine agonists (*n* = 2868)	**IRLS Responders**		
		Pramipexole: MD, −6.6 (−9.2 to −4.1) Ropinorole: MD, −3.6 (−4.8 to −2.5) Rotigotine: MD, −5.6 (−7.6 to −3.6)	–	–
		CGI Responders		
		Pramipexole: RR, 1.7 (1.4 to 2.0) Ropinorole: RR, 1.4 (1.3 to 1.5) Rotigotine: RR, 1.5 (1.2 to 1.9)	–	–
		Adverse Events		
		Pramipexole: 4.8% (2.0 to 8.7%) Ropinorole: 10.2% (2.6 to 22.1%) Rotigotine: 7.6% (1.3 to 18.5%)	–	–

CGI = Clinical Global Impression Improvement Scale (7-point global clinician rating of change of patient status since starting treatment; range very much worse to very much improved); IRLS = International Restless Legs Syndrome Study Group Rating Scale (10 questions assessing symptom severity and impact on activities of daily life; total score range 0 to 40); IV = intravenous; MD = mean difference; OR = odds ratio; PGI = Patient-assessed Global Impression Improvement Scale (7-point global patient rating of change of status since starting treatment; range very much worse to very much improved); PLMI = Periodic Limb Movement Index; RCT = randomized, controlled trial; RR = risk ratio.

** Studies from a systematic review described in the **Appendix** (available at www.annals.org). All studies ≥7 AMSTAR score (A Measurement Tool to Assess Systematic Reviews). CGI-I and PGI-1 responders are defined by clinician or patient assessment of "much" or "very much" improved on global impression scales.*

Table 4. **Recommended Pharmacologic Treatment for Patients With Moderate–Severe Restless Legs Syndrome**

Guideline	*Pramipexole*	*Ropinirole*	*Rotigotine*	*Gabapentin Enacarbil*	*Gabapentin*	*Pregabalin*	*Opioids*
European RLS Study Group, 2011 (3)	First-line	First-line	First-line	Second-line¶	Second-line	Second-line	Second-line
AASM, 2012 (5)	Standard*	Standard*	Standard*	Guideline†	Option‡	Option§	Guideline‖
Joint European, 2012 (55)**	"A" short; "B" long-term (0.25-0.75mg)	"A" short; "B" long-term (2-3mg)	"A" short and long-term (1-3mg)	"A", short-term 1200mg; probably effective long-term	"A" short-term; probably effect long-term	"A" short-term (150-450mg)	-
Willis Ekbom Disease Foundation, 2013 (30)	First-line	First-line	First-line	First-line	First-line	First-line	Intermittent or refractory
IRLS Study Group, 2013 (25)**	"A", 6 months; "B", 1 year	"A", 6 months; "B", 1 year	"A", 6 months; "B", 1 year	"B", 1 year	Insufficient evidence	"A", 1 year	Insufficient evidence

AASM = American Academy of Sleep Medicine; IRLS = International Restless Legs Syndrome.
¶ Not available in Europe, and this was considered as part of the European RLS Study Group recommendations.
** Standard = Large body of evidence and benefits clearly outweigh harms.*
† Guideline = Large body of evidence and uncertainty in balance between benefits and harms.
‡ Option = Small body of evidence and unclear harm–benefit balance.
§ Option = Small body of evidence and benefits closely balanced with harms.
‖ Guideline = Small body of evidence and benefits clearly outweigh harms.
*** Level A rating (established as effective, ineffective, or harmful) requires at least 1 convincing class I study, defined as an adequately powered, prospective, randomized, controlled, double-blind clinical trial in a representative population or an adequately powered systematic review of prospective, randomized, controlled clinical trials with masked outcome assessment in representative populations; or at least 2 consistent, convincing class II studies (prospective matched-group cohort study in a representative population with masked outcome assessment); level B rating (probably effective, ineffective, or harmful) requires at least 1 convincing class II study or overwhelming class III evidence. (All other controlled trials [including well-defined natural history controls or patients serving as their own controls] in a representative population, where outcome assessment is independent of patient treatment).*

RLS than in those with Parkinson disease. Other important adverse events include development of impulse control disorders, which manifest as uncontrollable or excessive gambling, spending, hypersexuality, or other behavioral addictions (30, 43). Therefore, all patients initiating dopamine agonists should be educated and closely monitored for the development of impulsive behaviors. These behaviors may escape detection, as some patients may be deceptive or lack insight, which could obscure these problems from others (44). Another critical consideration for longer-term treatment with dopamine agonists is augmentation. Augmentation is the appearance or worsening of RLS symptoms earlier in the day than was originally present, increased intensity of symptoms, or spread of symptoms to the arms (36, 43). Lack of use of validated protocols to diagnose augmentation in clinical research and delayed timing of augmentation (development typically occurs after at least 6 months of use, whereas most clinical studies are ≤3 months in duration) has led to wide variation in observed long-term augmentation rates.

Observational studies have documented augmentation rates of up to 65% at 10 years for pramipexole (45), 24% at 5 years for ropinirole (46), and 13% at 5 years for rotigotine (47).

Alpha-2 delta ligands

Alpha-2 delta ligands bind with high affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels and include gabapentin enacarbil, gabapentin, and pregabalin. Gabapentin enacarbil, a prodrug of gabapentin, is the only alpha-2 delta ligand with FDA approval specifically for RLS (**Table 2**).

39. Hornyak M, Scholz H, Kohnen R, et al. What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. Sleep Med Rev. 2014;18:153-64. [PMID: 23746768]
40. Zintzaras E, Kitsios GD, Papathanasiou AA, et al. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. Clin Ther. 2010;32:221-37. [PMID: 20206780]
41. Zhang W, Wang Y, Cong SY, et al. Efficacy and tolerability of pramipexole for the treatment of primary restless leg syndrome: a meta-analysis of randomized placebo-controlled trials. Neuropsychiatr Dis Treat. 2013;9:1035-43. [PMID: 23950645]

*Gabapentin enacarbil on a short-term basis (≤12 weeks) has been demonstrated in several randomized, control trials (RCTs) to significantly reduce RLS symptoms, periodic leg movements of sleep, and wakefulness after sleep and to improve subjective sleep quality (***Table 3***), and open-label extension studies demonstrate longer-term responses up to 52 weeks (48, 49).*

Gabapentin enacarbil's greater bioavailability than gabapentin is due to its rapid absorption via 2 high-capacity nutrient transporters throughout the intestine. It is a controlled-release formulation and is administered once daily, typically in the early evening, with food, which further increases bioavailability.

The efficacy of pregabalin for RLS has been established in 2 RCTs. The larger trial, by Allen and colleagues (36), was a landmark study because of its size, methodological rigor, and duration. It demonstrated pregabalin's (300 mg) superiority for RLS symptoms compared with placebo at 12 weeks (IRLS mean difference, –4.5 [95% CI, –5.9 to –3.2]; CGI responders, 71.4% vs.48.6%; P *value <0.001) and noninferiority to pramipexole (0.25 and 0.50) at 52 weeks. Notably, participants assigned to pregabalin also had a significantly lower rate of augmentation at 52 weeks than those assigned to the higher dose of pramipexole (1.7% vs. 9.0%;* P *value <0.001), a rate similar to that found for placebo, suggesting natural variation or progression, rather than augmentation. Most secondary sleep outcomes significantly improved with pregabalin compared with either dose of pramipexole.*

These data have informed more recent clinical guidelines but are not reflected in earlier guidelines, such as those by the European RLS Study Group and AASM, which accounts for some inconsistencies across recommendations (**Table 4**). Fewer data exist on gabapentin, although some trials have found efficacy, and small studies suggest that it may be as effective as ropinirole and levodopa. Gabapentin is poorly absorbed above 500 mg and thus divided doses (2 or 3 times per day) produce the best therapeutic response. Adverse effects of alpha-2 delta ligands include dizziness, somnolence, weight gain, and depression/suicidal ideation.

Recent expert consensus guidelines recommend the initiation of dopamine agonists in patients with very severe RLS, comorbid depression/dysthymia, and obesity/metabolic syndrome and alpha-2 delta ligands in patients with comorbid pain, anxiety, insomnia, previous impulse control disorder, or addiction (30).

Other medications

The data examining benzodiazepines for RLS are sparse, but these drugs have generally been found to be ineffective. Only one RCT has evaluated opioids for RLS. A recent study enrolled 306 patients with moderate–severe RLS and previous treatment failure and reported that oxycodone-naloxone twice daily (mean daily dose of oxycodone 22 mg and naloxone 11 mg) was superior to placebo at 12 weeks (50). The oxycodone-naloxone group experienced more treatment-related adverse events (73% vs. 43%), more severe adverse events (11% vs. 5 %), and a higher proportion of dropouts due to adverse events (15% vs. 7%) during the double-blind phase. During a 40-week open-label extension period, 112 of 197 participants (57%) had treatment-related adverse events. Given the high rates of participant dropout in this study and the high frequency of adverse events, few experts commonly recommend opiates for RLS, although some observational studies suggest that opioids improve RLS symptoms with low rates of dependence (45, 51, 52, 53). However, providers should exercise caution when considering prescribing opioids for RLS, which should only be considered after other strategies

42. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al; European Federation of Neurological Societies. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. Eur J Neurol. 2012;19:1385-96. [PMID: 22937989]
43. Wilt TJ, MacDonald R, Ouellette J, et al. Treatment for Restless Legs Syndrome. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Accessed at www.ncbi.nlm.nih.gov /books/NBK115385/ on 16 September 2015.
44. Weiss HD, Pontone GM. Dopamine receptor agonist drugs and impulse control disorders. JAMA Intern Med. 2014;174: 1935-7. [PMID: 25329734]
45. Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011;12: 440-4. [PMID: 21239226]
46. Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med. 2011;12: 431-9. [PMID: 21493132]
47. Oertel W, Trenkwalder C, Bene H, et al; SP710 study group. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011;10:710-20. [PMID: 21705273]
48. Ellenbogen AL, Thein SG, Winslow DH, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. Clin Neuropharmacol. 2011; 34:8-16. [PMID: 21242741]
49. Inoue Y, Uchimura N, Kuroda K, Hirata K, Hattori N. Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36:251-7. [PMID: 22036917]

are exhausted, the patient's potential for misuse of the medication is carefully assessed, and a sleep specialist has been consulted.

How should clinicians monitor patients?

Initially, doses should be titrated to the lowest effective dose, as tolerated, with close monitoring for side effects and dopaminergic-induced augmentation. Patients may not respond to first-line drugs. Those who do not improve should be reassessed for changes in aggravating factors, such as iron stores, lifestyle (sitting more), sleep patterns, use of other medications, or misuse of the prescribed medication. Medication rebound can occur with shorter-acting RLS medications (e.g., ropinirole). Natural progression and variation in the disease should also be considered, because large improvements in RLS symptoms, moderate improvements in quality of life, and small improvements in sleep outcomes have been observed in patients with RLS who were assigned to placebo (54). There is no standard approach for treating augmentation, but practice guidelines recommend splitting the dose of the drug, with additional dosing earlier in the day, or changing to a longer-acting agent in the same medication class (30). In some cases, dual treatment with different classes can be used. For individuals with progressive augmentation and increasingly early symptom onset, discontinuation of the dopaminergic agent and substitution with either an alpha-2 delta ligand or a high-potency opioid should be considered.

When should clinicians consider consulting a specialist?

A large proportion of patients with RLS do not require pharmacologic therapies or specialty evaluation. The benefits and risks of pharmacologic therapy in patients with mild RLS symptoms are unknown. Most patients with moderate–severe RLS have a sufficient therapeutic response and tolerate initial medication selection, as evidenced by clinical trial data, and thus may not require specialist care. Evaluation and treatment by a specialist (i.e., sleep or neurology) is recommended in cases of atypical presentation of symptoms, loss of efficacy of the initial treatment despite increased dosage, intolerable side effects, or augmentation (5). Referral to a sleep specialist or neurologist may also be warranted in cases of a coexisting sleep disorder, neurologic disorder, or other complex medical condition.

We conducted a systematic literature review (55, 56) of the efficacy of medication treatments of restless legs syndrome in adults ≥18 years of age (**Appendix**, available at www.annals.org).

50. Trenkwalder C, Beneš H, Grote L, et al; RELOXYN Study Group. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013;12:1141-50. [PMID: 24140442]
51. Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord. 2005;20:345-8. [PMID: 15580610]
52. Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. NCHS Data Brief. 2009:1-8. [PMID: 19796521]
53. Cheatle MD, Barker C. Improving opioid prescription practices and reducing patient risk in the primary care setting. J Pain Res. 2014;7:301-11. [PMID: 24966692]
54. Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. Brain. 2008;131:902-17. [PMID: 17932100]
55. Cornell JE, Laine C. The science and art of deduction: complex systematic overviews [Editorial]. Ann Intern Med. 2008;148:786-8. [PMID: 18490692]
56. Hunt DL, McKibbon KA. Locating and appraising systematic reviews. Ann Intern Med. 1997;126:532-8. [PMID: 9092319]

Treatment... Nonpharmacologic therapies are largely unproven and focus on distracting activities or planned ambulation. Despite anecdotal reports, there is no strong evidence that avoidance of putative triggers, such as specific medications, alcohol, or caffeine, alleviates symptoms. Furthermore, given the lack of evidence, the AASM and IRLS Study Group do not recommend monotherapy with iron supplementation as a standard of care, although other guidelines recommend consideration of iron supplementation on a case-by-case basis in patients with serum ferritin levels <45–75 μg/L. Pharmacologic treatment for RLS should be considered in patients with moderate–severe RLS and for those with intermittent, bothersome symptoms. First-line therapies include both dopamine agonists and alpha-2 delta ligands. Medications should be dosed before the expected start of bothersome symptoms, based on time of maximum concentration of the selected therapy (e.g., 1 hour before symptoms for ropinirole) and should be titrated to the lowest effective dose. Patients should be monitored closely for side effects. Patients who have loss of efficacy, adverse effects, or augmentation should be referred to a sleep clinician or neurologist with experience treating RLS.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend regarding the care of patients with RLS?

In 2015, the AASM published the first quality measures for managing adults with RLS (57). The evidence was based on expert judgment and has not been tested systematically. The quality measures focused on processes to improve the accuracy of RLS diagnosis, decrease symptom severity, and minimize treatment complications.

57. Trotti LM, Goldstein CA, Harrod CG, et al. Quality measures for the care of adult patients with restless legs syndrome. J Clin Sleep Med. 2015; 11:293-310. [PMID: 25700882] doi:10.5664/jcsm.4550

In the Clinic Tool Kit

Restless Legs Syndrome

Patient Information

www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm?css=print
National Institutes of Health.
www.aafp.org/afp/2008/0715/p243.html
American Academy of Family Practitioners.
www.cdc.gov/sleep/about_sleep/key_disorders.htm
Centers for Disease Control and Prevention.

Clinical Guidelines

www.aasmnet.org/resources/practiceparameters/treatmentrls.pdf
www.guideline.gov/content.aspx?id=38320
www.aafp.org/afp/2013/0215/p290.html
Medical guidelines for clinical practice for the diagnosis and treatment of restless legs syndrome.

WHAT YOU SHOULD KNOW ABOUT RESTLESS LEGS SYNDROME

What Is Restless Legs Syndrome?

Restless legs syndrome, or RLS, is a condition that causes uncomfortable feelings in the legs. RLS can also cause urges to move the legs that you can't control. These feelings and urges usually get worse during periods of rest. RLS symptoms can make it very hard to sleep. What causes RLS is as yet unknown, but other health conditions could make it more likely, including:

- Chronic kidney disease
- Low iron levels
- Pregnancy

Sometimes certain medicines may make symptoms worse. These include:

- Medicine for depression and other mental problems
- Medicines for nausea
- Certain cold and allergy medicines

What Are the Warning Signs?

Most symptoms of RLS are worse at night or while you are at rest, but can sometimes be felt during the day. These symptoms may include:

- An urge to move your legs that you cannot control
- Uncomfortable feelings in the legs
- Leg pain
- Leg jerks
- Trouble falling asleep or staying asleep
- Feeling tired during the day

How Is It Diagnosed?

Your doctor will ask questions about your symptoms, your family history, and any medicines you take and will examine you. He or she may also order blood tests to rule out other reasons for your symptoms.

How Is It Treated?

Because the cause of RLS is unknown, finding the right treatment can take time. Some treatment options are:

- Changing medicines that might be making your symptoms worse
- Lifestyle changes like forming good sleep habits, exercising regularly, and stretching before bed

- Massaging your legs, taking a hot bath, or using a heating pad or ice pack.

There are some medicines that are helpful in the treatment of RLS. Ask your doctor about the treatment option that's right for you.

Questions for My Doctor

- What is causing my symptoms?
- Which medicines will be best for me?
- Could RLS cause long-term damage?
- Could my symptoms go away by themselves?
- How can I form good sleep habits?
- I can't concentrate because of my RLS—what can I do?

Bottom Line

- RLS is a condition that causes uncomfortable feelings in your legs. It can also cause an urge to move your legs that you can't control. These feelings and urges are worse while you are at rest or during the night.
- Other symptoms of RLS can include leg pain, leg jerks, trouble falling asleep or staying asleep, and feeling tired during the day.
- To diagnose RLS, your doctor will ask about your medical history and examine you. Blood tests may be needed to rule out other conditions.
- There are several ways to manage your symptoms, including lifestyle changes, medicines, and other treatment options.

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

Medline Plus
https://www.nlm.nih.gov/medlineplus/restlesslegs.html

Restless Legs Syndrome Foundation
www.rls.org/about-rls

Patient Information

Appendix: Complex Systematic Literature Review Methods

We conducted a systematic literature review (56, 57) of the efficacy of medication treatments of restless legs syndrome in adults ≥18 years old according to PRISMA guidelines (**Appendix Figure**).

Given several recent comprehensive quantitative reviews, we focused on identifying and summarizing published meta-analyses for drug treatments for restless legs syndrome. We searched 4 databases: PubMed (National Center for Biotechnology Information), EMBASE (Elsevier), PsycINFO (EBSCO Publishing), and Cochrane Library (EBSCO Publishing). In addition to journal citations, PubMed produced reports from the AHRQ through NCBI Bookshelf. A medical librarian developed search strategies customized for the indexing and search utilities of each database. Strategies included both subject headings and free-text terms (see PubMed strategy). Searches covered literature indexed from database inception through March 2014. A validated search strategy filtered results to systematic reviews, meta-analyses and evidence-based guidelines when necessary. Results were limited to English language studies on adults.

The initial search yielded 143 articles on pharmacologic treatment of restless legs syndrome. Titles and abstracts were reviewed to identify quantitative reviews (meta-analyses), nonquantitative reviews, and other articles that met our inclusion criteria. Given recent proliferation of clinical trials investigating medications for treatment of restless leg syndrome, we limited our selection to reviews published within the past 5 years. From the original results, we identified 23 articles that potentially met our initial criteria. We further excluded 3 that were not in English, 4 that were not systematic reviews, 6 that were not systematic quantitative reviews, and 5 that were prior systematic quantitative reviews by the same study groups that included studies in more current or comprehensive quantitative reviews by the same study team. This left 5 meta-analyses for our summary. For all included articles, we summarized the number of reviewed studies and participants, the major review methods, and findings when >2 studies were synthesized.

PubMed Search Strategy: ((((Willis Ekbom[tw] OR Wittmaack-Ekbom[tw] OR restless legs[tw] OR "Restless Legs Syndrome"[Mesh]) AND ("therapy"[Subheading] OR "diet therapy"[Subheading] OR "drug therapy"[Subheading] OR "radiotherapy"[Subheading] OR "surgery"[Subheading] OR "Complementary Therapies"[Mesh] OR treatment[tw])))

This strategy was modified with appropriate subject and text-word terms used in the other databases. It was then combined with the validated strategy to identify meta-analyses, systematic reviews, and evidence-based guidelines.

Appendix Figure. **Summary of evidence search and selection.**