JAMA | Review

Restless Legs Syndrome
A Review

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IMPORTANCE Restless legs syndrome (RLS) is a sleep-related movement disorder that affects approximately 3% of US adults to a clinically significant extent and can cause substantial sleep disturbance.

OBSERVATIONS Restless legs syndrome is characterized by an overwhelming urge to move the limbs, typically the legs, often accompanied by unpleasant limb sensations (eg, achiness, tingling). Symptoms, provoked by immobility, are relieved while moving and are typically present or most severe in the evening or at night. Restless legs syndrome symptoms may lead to difficulty falling asleep, staying asleep, or returning to sleep. According to population-based studies, approximately 8% of US adults experience RLS symptoms of any frequency annually and 3% experience moderately or severely distressing symptoms at least twice weekly. Patients with RLS have impaired quality of life and elevated rates of cardiovascular disease (29.6% with coronary artery disease, stroke, or heart failure), depression (30.4%), and suicidal ideation or self-harm (0.35 cases/1000 person-years). Restless legs syndrome is common among patients with multiple sclerosis (27.5%), end-stage kidney disease (24%), and iron deficiency anemia (23.9%); during pregnancy and especially in the third trimester (22%); with peripheral neuropathy (eg, diabetic, idiopathic; 21.5%); and with Parkinson disease (20%). Other risk factors include family history of RLS, northern European descent, female sex (2:1 vs male sex), and older age (RLS prevalence of 10% in adults ≥65 years). Restless legs syndrome is diagnosed based on clinical history; polysomnography is not recommended for diagnosis. Iron supplementation with ferrous sulfate (325-650 mg daily or every other day) or intravenous iron (1000 mg) should be initiated for serum ferritin level less than or equal to 100 ng/mL or transferrin saturation less than 20%. If possible, medications associated with RLS, including serotonergic antidepressants, dopamine antagonists, and centrally acting H1 antihistamines (eg, diphenhydramine), should be discontinued. Gabapentinoids (eg, gabapentin, gabapentin enacarbil, pregabalin) are first-line pharmacologic therapy. In randomized clinical trials, approximately 70% of patients treated with gabapentinoids had much or very much improved RLS symptoms vs approximately 40% with placebo ($P < .001$). Dopamine agonists (eg, ropinirole, pramipexole, rotigotine) are no longer recommended as first-line medications due to the risk of augmentation, an iatrogenic worsening of RLS symptoms, which has an annual incidence of 7% to 10% with these medications. Patients who do not improve with first-line treatment or have augmented RLS often benefit from low-dose opioids (eg, methadone 5-10 mg daily).

CONCLUSIONS AND RELEVANCE Restless legs syndrome affects approximately 3% of adults and can have negative effects on sleep and quality of life. Initial management includes cessation of exacerbating medications, as well as iron supplementation for patients with low-normal iron indices. If medication therapy is indicated, gabapentinoids are first-line treatment.

JAMA. 2026;335(8):703-714. doi:10.1001/jama.2025.23247
Published online January 21, 2026.

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Restless legs syndrome (RLS), a sleep-related movement disorder, is present in approximately 3% of adults worldwide and is more common among women,[1] those of northern European ancestry,[2] and individuals with conditions associated with iron deficiency, including iron deficiency anemia and pregnancy (especially third trimester).[3,4] In addition to sleep disturbance, patients with RLS often have decreased health-related quality of life,[5] increased prevalence of mood and anxiety disorders,[6] and increased prevalence of cardiovascular disease (CVD).[7] This Review discusses the pathophysiology, epidemiology, risk factors and associated conditions, clinical presentation, assessment, diagnosis, treatment, and prognosis of RLS.

Methods

PubMed and Cochrane searches were performed for the period between January 1, 2010, and August 11, 2025, to identify English-language articles on the clinical presentation, epidemiology, diagnosis, pathophysiology, and management of RLS in adults; search terms included *restless legs syndrome* and *RLS*. Additional articles were identified through review of citations from these retrieved articles, as well as the authors' knowledge of the literature. Randomized clinical trials, systematic reviews and meta-analyses, and clinical practice guidelines were prioritized. Of 2277 articles identified, 117 were included, consisting of 65 observational studies, 21 systematic reviews and meta-analyses, 10 randomized clinical trials, 9 manuals and guidelines, 9 narrative reviews, and 3 other experimental studies (an uncontrolled clinical trial, a human study involving intentional sleep deprivation, and a mouse genetic study).[8-10]

Pathophysiology

Restless legs syndrome pathophysiology likely involves several factors, including abnormal iron metabolism, genetic predisposition, and increased dopaminergic activity in the brain.[11] Although serum iron indices are often normal in patients with RLS, low brain iron levels have been reported in individuals with RLS according to findings from autopsy,[12] magnetic resonance imaging,[13] transcranial ultrasonography,[14] and cerebrospinal fluid.[15] Analysis of postmortem tissue in patients with RLS demonstrates that low brain iron levels, frequently in the context of normal serum iron levels, may at least partially relate to dysfunction at the blood-brain barrier, with altered expression of iron transport proteins in both the brain microvasculature and choroid plexus.[16]

There is also strong evidence for a genetic predisposition.[17] Approximately half of patients with idiopathic RLS (ie, not associated with a systemic condition such as iron deficiency) have a first-degree family history of RLS.[18] Restless legs syndrome heritability of up to 70% has been estimated according to twin studies,[19] and an autosomal dominant–like pattern of inheritance appears to be present in most familial cases of RLS.[20] A recent meta-analysis of 3 genomewide association studies that included 116 647 patients with RLS and 1 546 466 control participants identified 164 risk loci, and the single nucleotide variation–based heritability of RLS was estimated to be 20%.[21] Important genes linked to RLS include *MEIS1,* which plays a role in nervous system and limb development and is strongly associated with insomnia symptoms in humans,[10,22,23] and *BTBD9,* which may play a role in iron homeostasis.[24,25]

Imaging studies using positron emission tomography and single-photon emission computed tomography suggest that patients with RLS have increased presynaptic dopaminergic activity, especially in the striatum.[26,27] Additionally, cerebrospinal fluid analyses revealed greater morning-to-evening changes in dopamine-related cofactors and metabolites in patients with RLS compared with controls, perhaps reflecting the evening or nighttime predominance of symptoms in patients with RLS.[28]

Furthermore, endogenous opioid deficiency may contribute to RLS symptoms; a recent study reported decreased cerebrospinal fluid levels of the endogenous opioid β-endorphin in patients with RLS (n = 42) compared with matched controls (n = 44), and particularly in those with painful symptoms.[29,30] Other alterations, including those in glutamatergic neurons, may also play a role in RLS pathogenesis.[31]

Epidemiology

Restless legs syndrome prevalence worldwide is estimated to be 1.9% to 4.6%.[1] Among US adults, approximately 8% experience RLS symptoms of any frequency in a year and 3% have moderately or severely distressing symptoms that occur at least twice weekly.[2]

Approximately two-thirds of patients have onset of RLS symptoms before age 45 years,[32] although most do not present for clinical evaluation until age 50 to 60 years because symptom severity is often initially mild and fluctuating. Approximately 10% of adults aged 65 years and older have RLS, and it is more common among women than men (female to male ratio of approximately 2:1) by age 65 years.[33] Despite the relatively high prevalence of RLS and growing awareness of the condition in both the general public and the medical community, RLS remains underdiagnosed, particularly in primary care settings.[34]

Risk Factors and Associated Conditions

Restless legs syndrome is commonly associated with iron deficiency[35]; in a cross-sectional study of 251 patients with iron deficiency anemia who presented to a hematology practice, 23.9% had RLS symptoms that occurred at least twice per week and were associated with moderate to severe distress, determined based on responses to the 13-item Cambridge-Hopkins Restless Legs Syndrome Questionnaire (discussed below).[4] More than 40% of patients with RLS without anemia have iron indices that are in the recommended range for iron supplementation (ferritin <100 ng/mL, transferrin saturation <20%, or both).[36,37]

Prevalence of RLS is also high in pregnancy. A 2018 systematic review and meta-analysis of 51 717 pregnant women reported a pooled prevalence of RLS across the 3 trimesters of 22% (95% CI, 17%-26%), with 8% (95% CI, 3%-12%) in the first trimester, 16% (95% CI, 7%-24%) in the second trimester, and 22% (95% CI, 15%-30%) in the third trimester.[3] Approximately 20% of women with RLS during pregnancy experience severe to very severe RLS symptoms.[38] Restless legs syndrome prevalence decreases to 4%

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Box 1. Descriptors of Restless Legs Syndrome (RLS) Symptoms

Ants crawling
Burning
Crazy legs
Creepy-crawly
Electric current
Fidgety (46%)
Irritating (56%)
Nagging (56%)
Painful (21%)
Restless (88%)
Shocklike feelings
Soda bubbling in veins
Tingling
Twitchy (63%)
Uncomfortable (78%)
Unpleasant (59%)

Numbers in parentheses represent percentages of patients with RLS who characterized symptoms with a given descriptor.[46,47]

Box 2. Restless Legs Syndrome (RLS) Diagnostic Criteria

Criteria A Through C Must Be Met

A. A complaint of an urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. These symptoms must
   1. begin or worsen during periods of rest or inactivity, such as lying down or sitting;
   2. be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and
   3. occur exclusively or predominantly in the evening or at night rather than during the day.
B. The above features are not solely accounted for by a condition that mimics RLS (eg, leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping).
C. The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

Further Considerations

1. The urge to move the legs may be present without any other distinct uncomfortable sensation. The arms or other parts of the body may also be involved.
2. For children, the description of these symptoms should be in the child's own words. Drawing the symptoms may be helpful if they cannot be verbalized.
3. When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
4. As a result of severity, treatment intervention, or treatment-induced augmentation, worsening of symptoms in the evening or at night may not be noticeable but must have been previously present.
5. The RLS criteria may be met in the context of certain medical conditions (eg, chronic kidney failure), in which case the separate diagnosis of RLS can still be made.
6. For certain research applications, such as genetic or epidemiologic studies, it may be appropriate to omit criterion C. If so, this omission should be clearly stated in the research report.

Adapted from the *International Classification of Sleep Disorders, Third Edition, Text Revision*.[48]

after childbirth, with approximately 75% of cases resolving within 1 month after delivery.[3]

Restless legs syndrome prevalence may be as high as 50% in patients with opioid withdrawal (eg, in opioid use disorder or after prescription opioid use for postsurgical pain).[39,40] A 2024 meta-analysis that included 50 cross-sectional studies, 5 cohort studies, and 2 case-control studies reported an RLS pooled prevalence of 24.0% (95% CI, 21.0%-26.0%) among 12 573 patients with end-stage kidney disease.[41] Estimated RLS prevalence among patients with peripheral neuropathy of varying etiologies (eg, diabetic, idiopathic) is 21.5%, although distinguishing neuropathic symptoms from those of RLS can be difficult.[42] Restless legs syndrome affects approximately 27.5% of patients with multiple sclerosis,[43] 20% of patients with Parkinson disease (particularly after the initiation of dopaminergic medications),[44] and 16% of patients with obstructive sleep apnea.[45]

Clinical Presentation

The essential clinical features of RLS include an urge (or need) to move the legs (or arms) that is commonly associated with paresthesia (**Box 1**)[46,47] that is present at rest (sitting or lying down), improves with movement (but often returns with immobility), is most severe in the evening or at night, and is not adequately explained by conditions in the differential diagnosis (**Box 2**).[48] For patients with severe RLS, relief with movement is only partial, and symptoms may be present throughout the day, making nighttime worsening of symptoms less apparent.

Restless legs syndrome varies in severity and frequency, ranging from mild symptoms less than once annually (eg, with prolonged immobility on long airplane rides) to severe symptoms nearly continuously. Although the symptoms of RLS are most commonly present bilaterally in calves or thighs, they can occur unilaterally, in the feet, and even in the torso or upper extremities. In moderate to severe cases, RLS symptoms are highly distressing and make it almost impossible to remain immobile. Overnight sleep deprivation worsens RLS symptoms throughout the day.[9]

Patients often seek care when RLS causes at least moderate distress and sleep disturbance greater than or equal to 2 times per week.[2,49] Analysis of surveys completed by 551 patients with RLS demonstrated that RLS symptoms resulted in 69% taking at least 30 minutes to fall asleep and 60% awakening 3 or more times nightly.[49] A 2022 meta-analysis of 31 case-control studies using polysomnography reported that compared with healthy controls, patients with RLS had reduced total sleep time (358 vs 386 minutes; n = 1636; $P < .001$), decreased sleep efficiency (ie, the percentage of time sleeping while in bed; 75% vs 84%; n = 1642; $P < .001$), and increased wake time after sleep onset (81 vs 54 minutes; n = 682; $P < .001$).[50] In questionnaires administered to 416 patients with RLS, commonly reported symptoms included daytime sleepiness (32.2%), difficulty concentrating the next afternoon (19.2%), and disturbance of daily activities (40.1%),[2] likely due to disruptions in sleep.[51]

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Box 3. Commonly Asked Questions About Restless Legs Syndrome (RLS)

How is restless legs syndrome diagnosed?
RLS is a clinical diagnosis based on a self-reported urge to move the limbs (typically the legs) that is present at rest, improves while moving, and is most prominent in the evening or at night.

What are initial treatment strategies for patients with RLS?
Current evidence-based guidelines recommend cessation of exacerbating medications (eg, serotonergic antidepressants, dopamine antagonists, centrally acting H1 antihistamines) and recommend iron supplementation for patients with serum ferritin level less than or equal to 100 ng/mL (although some clinical data suggest treating if <300 ng/mL) or transferrin saturation less than 20%.

Why are dopaminergic medications not US guideline recommended as daily treatment for RLS?
Although initially efficacious, dopaminergic medications often worsen RLS symptoms over time, called augmentation, a condition characterized by earlier RLS symptom onset during the evening or daytime and an overall worsening of symptom severity (incidence of 7%-10% annually). Gabapentinoids are preferred for the daily treatment of RLS because their efficacy is similar to that of dopaminergic medications and they do not cause augmentation.

Additionally, 45.7% of the 416 patients reported a sensory symptom (eg, uncomfortable feelings, pain) as their most troublesome symptom.[2]

Conditions Associated With RLS

Restless legs syndrome is commonly associated with mood and anxiety disorders. A 2024 systematic review and meta-analysis (n = 2039 patients with RLS) reported that the prevalence of significant depression symptoms, defined mostly by questionnaire thresholds (eg, Patient Health Questionnaire–9 score ≥10) in 11 included observational studies, was 30.4% (95% CI, 20.6%-42.4%).[52] A 2005 observational study reported that compared with community respondents from a nationally representative sample without RLS (n = 2265), patients with RLS (n = 130) had a higher 12-month prevalence of panic disorder (8.5% in patients with RLS vs 2.1% in patients without RLS; odds ratio, 4.7; 95% CI, 2.1-10.1), generalized anxiety disorder (8.5% vs 2.3%; odds ratio, 3.5; 95% CI, 1.7-7.1), and major depression (17.7% vs 8.7%; odds ratio, 2.6; 95% CI, 1.5-4.4).[6]

Although results have been mixed,[53] observational studies have revealed an increased prevalence of CVD in patients with RLS, including a cross-sectional study (n = 3433) that reported a prevalence of 29.6% (CVD defined as history of coronary artery disease, stroke, or heart failure) in those with RLS compared with 19.5% in those without RLS (adjusted odds ratio, 2.07; 95% CI, 1.43-3.00).[7] Restless legs syndrome is also associated with CVD risk factors, including hypertension. A cross-sectional study including 65 544 women (41-58 years) reported that the prevalence of hypertension was 33% in women who had RLS symptoms at least 15 times per month vs 21% in women without RLS.[54] Compared with that of women without RLS symptoms, the adjusted odds ratios for hypertension were 1.06 (95% CI, 0.94-1.18) for women with RLS symptoms 5 to 14 times per month and 1.41 (95% CI, 1.24-1.61) for those with RLS symptoms at least 15 times per month (*P* trend <.001). Mechanisms underlying the potential association between RLS and CVD include sleep disturbance, a well-documented risk factor for CVD,[55] and periodic limb movements of sleep (PLMS), which have been associated with incident CVD risk.[56]

PLMS

Although polysomnography is not recommended for diagnosis of RLS, some patients may undergo this testing and have PLMS, which are involuntary and repetitive movements identified by electromyography on overnight polysomnography. The movements occur at 15- to 30-second intervals during sleep and usually affect the lower leg but can involve the entire leg or the upper extremities.[57] These movements are distinct from the waking subjective urge to move that is the central feature of RLS. Approximately 30% of PLMS are associated with brief (<15-second) arousals on electroencephalogram, and PLMS are also associated with elevations in heart rate and blood pressure.[58,59] Periodic limb movements of sleep are observed in most patients with RLS who undergo overnight polysomnography and are regarded as the motor sign of RLS. However, high rates of PLMS are observed in other medical conditions such as congestive heart failure and multiple sclerosis,[60,61] in individuals taking serotonergic reuptake inhibitors,[62] and in healthy adults older than 50 years.[63] A community-based sample of 592 adults from the general population who underwent polysomnographic assessment to determine the prevalence of PLMS found that 22.5% of those with frequent PLMS (>15/h) reported RLS symptoms compared with 5.5% of participants without frequent PLMS.[64]

Assessment and Diagnosis

Restless legs syndrome is a clinical diagnosis based on the patient's description of the specific circumstances that provoke and relieve symptoms and their time-of-day variation (Box 2, **Box 3**, and **Figure 1**).[48] Clinicians should also ask about a family history of RLS and about use of medications that can initiate or exacerbate RLS (eg, centrally acting H1 antihistamines, serotonergic antidepressants, dopamine antagonists).[65,66] The differential diagnosis of RLS includes multiple conditions, most commonly anxiety, arthritis (eg, osteoarthritis, inflammatory arthritidies), and neuropathy (**Table 1**). All patients with RLS should undergo testing of serum iron indices (eg, ferritin, iron, total iron-binding capacity). Overnight polysomnography is not indicated for diagnosis of RLS.

Assessing RLS

The Cambridge-Hopkins Restless Legs Syndrome Questionnaire is a 22-item (or a commonly used 13-item short-form version) validated self-administered questionnaire that assesses the presence of clinical features of RLS described earlier.[67] In accordance with responses, patients can be categorized as having definite, probable, or no RLS. A validation study (n = 185) reported that this questionnaire had a high sensitivity (87%) and specificity (94%) compared with structured diagnostic interviews with qualified RLS experts.[67] Although the questionnaire is an effective RLS assessment tool, a clinical interview is required for diagnosis, even for patients with definite or probable RLS according to the questionnaire.[68]

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Figure 1. Evaluation of Restless Legs Syndrome

Clinical interview for diagnosis of restless legs syndrome (RLS)

Essential diagnostic criteria ("URGED")
- **U**rge to move the limbs (usually legs)
- Urge is present at **R**est
- Symptoms **G**et better with movement
- **E**vening or nighttime onset or worsening of symptoms
- **D**ifferential diagnosis does not explain symptoms

Risk factors
- Female sex (2:1 vs male sex)
- Older age (most do not present until age 50-60 y)
- Relative(s) with RLS (approximately half of patients have a first-degree relative with RLS)
- Use of certain medications (eg, antihistamines, serotonergic antidepressants, dopamine antagonists)

Other common features
- Unpleasant sensations (eg, achy, tingling) often accompanied by an urge to move limbs
- Difficulty falling asleep, staying asleep, or returning to sleep: primary reason patients seek medical care
- Daytime sleepiness (32%)
- Depression (30%)
- Difficulty concentrating (19%)
- Anxiety disorders (17%)

Conditions with high RLS prevalence
- Opioid withdrawal (50%)
- Multiple sclerosis (27.5%)
- End-stage kidney disease (24%)
- Iron deficiency anemia (24%)
- Pregnancy: first trimester (8%), second trimester (16%), third trimester (22%)
- Neuropathy (eg, diabetic, idiopathic [21.5%])
- Parkinson disease (20%)
- Obstructive sleep apnea (16%)

↓

Other assessments for diagnosis of RLS
- Blood testing: low serum ferritin and/or transferrin saturation
- Physical examination: can help rule out RLS mimics (eg, neuropathy)
- RLS screening questionnaires: follow-up interview should be performed
- Polysomnography: can provide information about sleep-related conditions (eg, periodic limb movements of sleep)

Table 1. Restless Legs Syndrome (RLS) and Common Mimics in Adults[a,b]

Disorder/mimic	RLS	Neuropathy	Anxiety	Arthritides (eg, OA, RA)	Nocturnal leg cramps	Positional discomfort	Akathisia
Description of symptoms	Urge to move legs (and sometimes arms), often with uncomfortable sensations	Pain, numbness, burning, or electrical sensations in legs or arms	Agitation accompanied by worry or unease, without sensory discomfort	Pain, discomfort, or stiffness in joints	Sudden and painful sustained contractions limited to the lower extremities	Extremity "asleep" from compression	Inner whole-body restlessness
Worse at night	Yes	Oftentimes	No	Not typically; may be worse in morning	Yes	No	No
Relieved by movement	Yes, with standing or walking	No	Possibly	Dependent on etiology	Yes, stretching helps	Yes, with simple change in position	Yes
Possible physical examination findings		Abnormal neurologic examination or nerve conduction study result	Tachycardia, tremor, diaphoresis	Joint effusion, erythema; warmth may be present			Body rocking movements, fidgeting
Additional features	PLMS on PSG; family history often present	Can coexist with RLS	May have history of anxiety disorder	Imaging may support diagnosis			Associated with dopamine antagonist use

Abbreviations: OA, osteoarthritis; PLMS, periodic limb movements of sleep; PSG, polysomnography; RA, rheumatoid arthritis.

[a] Ordered left to right based on authors' perceptions of how often these are mistaken for RLS.

[b] Blank cells indicate that there was no pertinent information to include.

Management

Initial Management

Discontinuing exacerbating medications and managing medical conditions that contribute to RLS can ameliorate or eliminate RLS symptoms in some patients (Box 3; **Figure 2**).[69] Restless legs syndrome symptoms may resolve after kidney transplant. A small observational study of 11 patients with RLS and treated with hemodialysis reported that all had resolution of RLS symptoms within 1 to 21 days after kidney transplant.[70] Similarly, treatment of obstructive sleep apnea may improve RLS symptoms.[71] Alcohol use may exacerbate RLS and thus should be avoided or limited.[72] Behavioral methods to manage symptoms include daytime exercise (eg, lower-body resistance training and treadmill walking 3 times per week), avoiding excess immobility, warm baths or showers, and stretching before bed.[73,74]

Iron Supplementation

Iron supplementation (with ferrous sulfate 325-650 mg orally or iron 1000 mg intravenously) is currently guideline-recommended first-line treatment for RLS for patients who have a serum ferritin concentration less than or equal to 100 ng/mL (although some clinical data suggest treating if <300 ng/mL)[75,76] or transferrin saturation less than 20% (**Table 2**).[37,77-85] Due to the poor absorption of oral iron with serum ferritin level greater than or equal to 75 ng/mL, intravenous iron is recommended for individuals with a ferritin level of 75 to 100 ng/mL or for those who do not tolerate oral iron, do not absorb it, or have contraindications to it.[37] The most well-studied form of intravenous iron is ferric carboxymaltose, although intravenous iron dextran is also commonly used.[8] In combined data from 2 randomized clinical trials with follow-up periods ranging from 4 to 24 weeks, 48% of 83 participants with RLS were much or very much improved after treatment with ferric carboxymaltose compared with 18% of 70 participants with placebo ($P < .001$).[77] A trial involving

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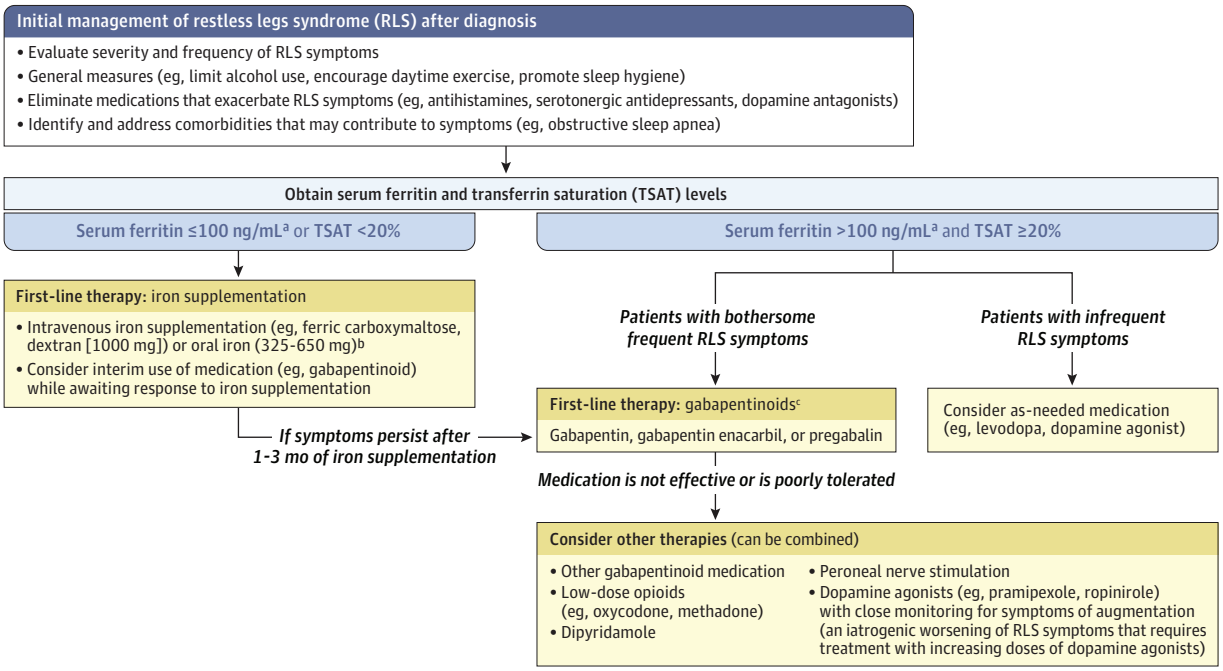
Figure 2. Management of Restless Legs Syndrome



Adapted from Manconi et al.[69]

[a]Serum ferritin level should be interpreted flexibly, and some data suggest treating if ferritin level is less than 300 ng/mL.

[b]Intravenous iron is recommended for patients with a ferritin level of 75 to 100 ng/mL or for those who do not tolerate, do not absorb, or have contraindications to oral iron.

[c]Gabapentinoids may not be appropriate first-line agents for patients for whom adverse effects are of particular concern (eg, weight gain, falls, depression or suicidal ideation).

patients with iron deficiency anemia and RLS reported similar RLS symptom improvement at week 6 among those randomized to oral iron (n = 46; 75%) vs intravenous iron ferumoxytol (n = 48; 68%) (P = .55). However, patients taking oral iron had more adverse effects (mostly gastrointestinal) than those taking intravenous iron (55% vs 11%).[86] To avoid hepatic iron overload, intravenous iron should not be administered if serum ferritin level is greater than 300 ng/mL or transferrin saturation is greater than 45%. Maximum symptom benefit may take 1 to 3 months, even with intravenous iron.[78]

Pharmacologic Approaches to RLS

Initial approaches to RLS medication management by both generalists and specialists should include assessment of the frequency, timing, and severity of symptoms to establish whether intermittent or daily treatment is warranted and to determine optimal timing of medications. A shared decision-making model is strongly encouraged. If only intermittent treatment is indicated (eg, symptoms present only when on long airplane or car rides), as-needed medications may be appropriate. For most patients, RLS treatments are taken in the evening or before bedtime to treat nighttime symptoms. Extended-release medication formulations should be reserved for patients with bothersome RLS symptoms lasting more than 8 hours per day.

Gabapentinoids

Gabapentinoids (also known as $\alpha_2\delta$ calcium-channel ligands), including gabapentin, pregabalin, and gabapentin enacarbil, were recommended in recent evidence-based guidelines as first-line medications for RLS, although gabapentin enacarbil is the only US Food and Drug Administration (FDA)–approved gabapentinoid medication for RLS.[37,87] A 2025 meta-analysis found that 73% of patients were much or very much improved after treatment across 7 randomized clinical trials with gabapentin enacarbil vs 39% with placebo (n = 1632; P < .001), and similar results were observed across 2 randomized clinical trials with pregabalin (69% vs 43%; n = 493; P < .001).[77] A crossover study of 24 patients with RLS reported that compared with those randomized to placebo, individuals randomized to gabapentin had improved polysomnographically measured total sleep time (6.0 vs 5.5 hours; P = .01) and sleep efficiency (84.7% vs 74.9%; P < .001) at 6 weeks (mean daily gabapentin dosage at the end of the treatment period = 1855 mg [SD, 105.6]).[88] Participants also had lower posttreatment scores on the Pittsburgh Sleep Quality Index (minimal clinically important difference commonly 2.5) with gabapentin (mean [SD], 6.4 [0.42] vs 9.3 [0.42] compared with mean baseline scores of 9.7; P < .001), indicating better subjective sleep quality.[88,89] Gabapentin (but not pregabalin or gabapentin enacarbil) is poorly absorbed above doses of 600 mg, and thus dosing may be required more than once in the evening to achieve optimal serum levels and efficacy. Gabapentinoids may also treat conditions commonly associated with RLS, such as insomnia, anxiety, and neuropathy. However, gabapentinoids can cause adverse effects, including gait instability, cognitive impairment, depression, suicidality, somnolence, dizziness, and weight gain, limiting tolerability in some patients.[77]

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Table 2. Treatments for Restless Legs Syndrome (RLS)[a]

Treatment	Recommended dose range for RLS, mg	CGI-I score responder difference vs placebo/control, % (95% CI)[b,c]	IRLS score mean difference vs placebo/control (95% CI)[c,d]	AASM recommendation[e]	Adverse effects
Treatments strongly or conditionally recommended for RLS					
Gabapentinoids ($\alpha_2\delta$ calcium-channel ligands)					
Gabapentin	300 to 3600 daily		−8.40 (−12.00 to −4.80)	Strong for	Somnolence (10%-25%),[77] dizziness (15%-19%),[77] cognitive disturbance, depression, suicidal ideation, weight gain
Gabapentin enacarbil	600 to 1200 daily	34 (24 to 45)	−4.93 (−6.85 to −3.02)	Strong for	
Pregabalin	75 to 600 daily	26 (17 to 34)	−4.81 (−6.21 to −3.42)	Strong for	
Iron[f]					
IV ferric carboxymaltose	1000 to 1500 in 1 or 2 doses	30 (16 to 44)	−7.43 (−11.89 to −2.97)	Strong for	Headache (12%),[78] nausea (5%),[78] flushing, hypersensitivity reaction, anaphylaxis risk (<0.0005%), hypophosphatemia (particularly with FCM), irritation at injection site
IV ferumoxytol	1020 in 1 or 2 doses		−7.90 (−11.74 to −4.06)	Conditional for	
IV LMW iron dextran	1000, single dose			Conditional for	
Oral iron (ferrous sulfate)	325 to 650 daily or every other day		−9.20 (−15.23 to −3.17)	Conditional for	Constipation (12%), diarrhea (8%), metallic taste, nausea (11%)[79]
Opioids					
Buprenorphine	0.5 to 6 daily			Conditional for	Constipation (47%), drowsiness/fatigue (23%), itching (19%), sweating (17%), stimulation/wakefulness (9%)[80]
Methadone	2.5 to 20 daily			Conditional for	
Oxycodone	5 to 40 daily	32 (21 to 43)[g]	−5.60 (−8.18 to −3.02)[g]	Conditional for	
Nonpharmacologic					
Peroneal nerve stimulation[h]	NA	34 (21 to 46)[g]	−3.40 (−5.02 to −1.78)[g]	Conditional for	Administration site irritation (9%), discomfort (28%)[81]
Treatments conditionally recommended against for RLS					
Dopaminergics[i]					
Levodopa	100 to 200 daily			Conditional against[j]	Augmentation (7%-10% annually),[82] somnolence (8%-15%),[77] dizziness (5%-11%),[77] impulse control disorders (10%-20%),[83] nasal stuffiness, nausea
Pramipexole	0.125 to 0.5 daily	23 (18 to 27)	−4.86 (−6.20 to −3.52)	Conditional against[j]	
Ropinirole	0.25 to 2 daily	18 (13 to 23)	−3.98 (−5.36 to −2.60)	Conditional against[j]	
Transdermal rotigotine	1 to 3 daily	11 (0 to 22)	−4.67 (−6.18 to −3.16)	Conditional against[j]	Application site reaction (34%),[77] in addition to other dopaminergic adverse effects

Abbreviations: AASM, American Academy of Sleep Medicine; CGI-I, Clinical Global Impressions–Improvement scale; FCM, ferric carboxymaltose; IRLS, International Restless Legs Syndrome Study Group Rating Scale; IV, intravenous; LMW, low molecular weight; NA, not applicable.

[a] Blank cells indicate no data available.

[b] The CGI-I, a commonly used tool in clinical trials, measures therapy effect.[84] At the end of the treatment period, a clinician interviews the patient and rates whether he or she is very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, or very much worse compared with before treatment (exact wording may vary). Patients rated as very much improved or much improved are commonly called responders. The responder difference represents the percentage of responders in the treatment group vs the percentage of responders in the control group. A commonly used clinical significance threshold is greater than 15% more responders than placebo or sham.

[c] From analyses performed for 2025 AASM systematic review, meta-analysis, and Grading of Recommendations Assessment, Development, and Evaluation assessment[77]; analyses for adults with RLS specifically in randomized clinical trials, across all tested doses.

[d] The IRLS is the most common and well-validated scale assessing RLS severity and treatment effects.[85] The questionnaire is completed by the patient and scores range from 0 (no RLS symptoms in the past week) to 40 (very severe RLS symptoms in the past week). A commonly used clinical significance threshold vs placebo is −3 points.

[e] Recommendations from 2025 AASM clinical practice guideline for adults with RLS.[37]

[f] Consensus guidelines suggest supplementation of iron for adults with RLS only for those with appropriate iron status (ie, oral or IV iron if serum ferritin level <75 ng/mL or transferrin saturation <20%; only with IV iron if serum ferritin level between 75 and 100 ng/mL).

[g] In patients with treatment-refractory RLS.

[h] Generally used as a supplemental RLS treatment (ie, in addition to agents listed above).

[i] Maximum US Food and Drug Administration–approved dosages for dopaminergics: pramipexole, 0.5 mg/d; ropinirole, 4.0 mg/d; transdermal rotigotine, 3.0 mg/d.

[j] Although dopaminergics have been conditionally recommended against in recent consensus guidelines, there are certain situations in which their use may be appropriate.

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Dopaminergics

Three dopamine agonists are FDA approved for treatment of RLS: ropinirole, pramipexole, and rotigotine. Across 12 randomized clinical trials, primarily in studies of 6 to 12 weeks' duration, 67% of patients were much or very much improved after treatment with pramipexole compared with 44% treated with placebo (n = 3436; $P < .001$), with slightly smaller effect sizes observed across 5 randomized clinical trials with ropinirole (61% vs 43%; n = 1428; $P < .001$) and 2 randomized clinical trials with rotigotine (67% vs 56%; n = 347; $P = .05$) (Table 2).[77] Similar to gabapentinoids, dopaminergics improve subjectively and polysomnographically measured sleep. A randomized clinical trial of 41 patients with RLS reported improvements in subjective sleep quality, measured by mean (SD) Pittsburgh Sleep Quality Index change compared with baseline (−4.3 [4.0] vs −0.4 [3.9]; $P = .002$) after 6 weeks of treatment with pramipexole vs placebo.[90] A meta-analysis found a mean difference of improvement in polysomnographically measured sleep efficiency of 4.53% with dopamine agonists vs placebo (95% CI, 2.00%-7.06%; $I^2 = 48\%$; $P < .001$).[91]

Although efficacious in the short term, daily long-term use of dopaminergic agonists can result in iatrogenic worsening of RLS, termed *augmentation,* characterized by increasingly earlier time of symptom onset, increased severity of symptoms, and development of symptoms in the upper extremities.[92] Augmentation typically develops slowly, with an incidence rate of approximately 7% to 10% per year,[82] and is often preceded by loss of efficacy of dopaminergics, requiring escalation of initially efficacious doses progressively earlier in the day,[93] which then increases the incidence and severity of RLS symptoms. In addition, dopaminergic medications, particularly at higher doses, can cause impulse control disorders, consisting of compulsive behavior (eg, spending, gambling, sexual), in 10% to 20% of patients with RLS.[83]

Comparison of Gabapentinoids and Dopaminergics

A network meta-analysis comparing gabapentinoids with dopaminergic agonists reported no statistically significant difference in efficacy (based on symptom severity scores) between agents in these 2 classes of medication.[94] There is no evidence of augmentation with gabapentinoids, including a 1-year study of pregabalin and pramipexole.[95] Given gabapentinoids' comparable efficacy and more favorable adverse effect profile, current US guidelines recommend them over dopaminergic agents as first-line daily treatments for RLS.[37,87] In addition, the most recent guidelines from the American Academy of Sleep Medicine recommended that dopaminergics not be prescribed as standard daily treatment of RLS due to the risk of augmentation of symptoms with long-term treatment (Box 3).[37] However, both generalist and specialist clinicians can consider prescribing dopamine agonists for long-term treatment if gabapentinoids are ineffective or not tolerated due to adverse effects such as weight gain, falls, or worsening depression. To minimize the risk of augmentation and impulse control disorders, maximum daily doses of dopaminergic medications should not exceed 0.5 mg for pramipexole, 2.0 mg for ropinirole, and 3.0 mg for rotigotine. Furthermore, for patients with occasional intermittent RLS symptoms (eg, during long airplane or car rides), as-needed use of low-dose dopaminergic medications (such as levodopa and ropinirole) may be appropriate.

Low-Dose Opioids

Consensus guidelines recommend low-dose opioids for patients with medication-refractory RLS (eg, those who do not improve with or cannot tolerate first-line medications) or augmented RLS.[37] In a 12-week, randomized, placebo-controlled trial that included 276 patients with refractory RLS, 67% were much or very much improved with twice-daily prolonged-release oxycodone-naloxone (mean [SD] daily dose = 21.9 [15.0] mg oxycodone/11.0 [7.5] mg naloxone) compared with 35% in the placebo group ($P < .001$).[96] For patients with RLS symptoms for more than 10 hours per day, low doses of the long-acting opioids methadone (2.5-20 mg daily) or buprenorphine (0.5-6 mg daily), which are approximately 10% of common treatment doses for chronic pain or opioid use disorder, are recommended by current treatment guidelines (Table 2).[80,97,98] Common adverse effects of opioids include constipation, daytime sleepiness, and itching. Although current evidence suggests a relatively low risk of misuse, overdose, or both in patients treated with opioids for RLS, careful risk assessment before prescribing is important.[99]

Peroneal Nerve Stimulation

A high-frequency peroneal nerve stimulation device worn on the lower legs bilaterally and typically used approximately 30 to 60 minutes in the evening before or at bedtime has recently demonstrated benefit as a supplemental treatment for patients with medication-refractory RLS. In a 2023 randomized clinical trial of 133 patients with medication-refractory RLS (with 90% taking concurrent pharmacologic therapy for RLS with gabapentinoids, dopaminergic medications, or other medications), 45% of patients were rated by a clinician as much or very much improved after 4 weeks of peroneal nerve stimulation compared with 16% in the sham group ($P < .001$).[81]

Management of RLS Augmentation From Dopaminergic Medications

Augmented RLS is difficult to manage and should be treated by sleep medicine specialists (often neurologists, pulmonologists, or psychiatrists), if possible. Patients with RLS augmentation often are taking dopaminergic medication doses above FDA-recommended maximums for RLS.[100] Tapering of dopaminergic medications, even by small amounts, often leads to a substantial rebound in RLS symptoms and may cause dopamine agonist withdrawal syndrome. This syndrome, which is associated with dopamine agonist dose reduction or discontinuation, is characterized by increased anxiety, depression, and suicidal ideation.[101] Studies also suggest that first-line RLS treatments (eg, gabapentinoids, intravenous iron) may be less efficacious for patients with RLS augmentation.[102,103] Moreover, patients and clinicians may have concerns about use of low-dose opioids because of stigma associated with these medications and the risk of addiction.

To our knowledge, there are no clinical trials examining the relative efficacy of various approaches to RLS augmentation. The initial approach involves mitigation of factors that can contribute to worsening symptoms, such as iron deficiency and medications that worsen RLS.[87,98,104] For patients for whom these interventions are inappropriate or ineffective, guidelines recommend initial addition of a gabapentinoid to the dopamine agonist and then very slow down-titration of the dopamine agonist (ie, 10%-25% of the dose every 2-4 weeks). If a gabapentinoid is not effective in controlling

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RLS symptoms, is poorly tolerated, or does not allow substantial reduction or elimination of the dopaminergic, low-dose long-acting opioid medications such as methadone or buprenorphine are usually prescribed. A retrospective case series of 63 patients with RLS augmentation who were treated with this strategy demonstrated that 78% had much or very much improvement in RLS symptoms, and 59% were able to discontinue dopamine agonists during a mean of 9 months (SD, 9.6 months).[100] A prospective longitudinal observational registry study of 500 patients, most with a history of augmentation, who were taking opioids for RLS demonstrated stable symptom severity and no escalation of opioid dose in 50% of participants during 5 years and a median increase of only 15 morphine milligram equivalents (equivalent to methadone 3.2 mg or oxycodone 10 mg) for those with increased opioid dose.[105]

Prognosis

More than 60% of patients with RLS have at least a 50% decrease in symptom severity with gabapentinoid or dopaminergic therapy.[106] Even with effective therapy, however, many patients report persistent RLS symptoms, difficulty falling and staying asleep, and mood and anxiety symptoms.[80,107]

Restless legs syndrome severity can fluctuate[108] and often worsens in response to a variety of factors, such as depression and anxiety, immobility, pain, triggering medications, and iron deficiency. Symptoms of RLS often increase with age, especially in patients with severe disease; however, remissions can occur, particularly in milder cases.[108,109]

A prospective study of 56 399 US women reported that 3.6% of participants with RLS developed clinical depression during a 6-year period (7.1 cases per 1000 person-years) compared with 2.2% of those without RLS (multivariate-adjusted relative risk, 1.49; 95% CI, 1.06-2.10).[110] Moreover, a US longitudinal cohort study of participants without a history of suicide or self-harm, CVD, or cancer at baseline reported an incidence rate of suicide and self-harm of 0.35 cases per 1000 person-years in patients with RLS (n = 24 179) vs 0.11 per 1000 person-years in those without RLS (n = 145 194; hazard ratio adjusting for potential confounders including depression, 2.66; 95% CI, 1.70-4.15).[111]

In a prospective cohort study that followed 18 425 US men without diabetes, arthritis, and kidney failure for 8 years, mortality was 24.8% for those with RLS vs 14.6% for those without RLS ($P < .001$ after adjusting for age, sex, and comorbidities, including cancer).[112] In a study of 204 patients with end-stage kidney disease, those with RLS had lower 1-year survival (82% vs 91%) and 2-year survival (62% vs 72%) compared with individuals without RLS ($P < .02$ after adjusting for age, sex, and years receiving dialysis).[113]

Treatment of RLS may be associated with decreased CVD risk. A 2021 prospective cohort study with 3.4 years of follow-up that included 16 694 patients receiving treatment for RLS (including dopaminergics, gabapentinoids/anticonvulsants, or opioids) and 7505 patients with RLS who were not receiving treatment reported that RLS treatment was associated with a 13% lower incident CVD risk (95% CI, 4%-20%) after adjusting for factors including age, sex, geographic region, and comorbidities.[114]

Practical Considerations

Restless legs syndrome is often underdiagnosed and insufficiently treated.[115] Misdiagnosis of sleep disturbance as insomnia rather than RLS and subsequent treatment with sedating agents such as benzodiazepine receptor agonists (eg, zolpidem) can cause sleep-related eating disorder, characterized by recurrent episodes of eating, drinking, or both with impaired consciousness that occur after the onset of sleep.[116] Additionally, for patients with RLS and obstructive sleep apnea, treatment adherence with continuous positive airway pressure can be challenging due to difficulty remaining immobile. All patients prescribed a dopamine agonist (which includes approximately 60% of those currently treated for RLS)[117] should be informed of the risk of developing augmentation symptoms with long-term daily use and should have regular clinical follow-up to monitor symptoms. Online RLS information for clinicians can be found at http://www.rlscurbside.org and http://www.irlssg.org, and information for patients can be accessed at http://www.rls.org.

Limitations

This review has several limitations. First, high-quality data are lacking for several RLS topics, including the role of nonpharmacologic treatments. Second, the literature search was limited to English-language publications and may have missed some relevant articles. Third, we focused on RLS in adults and did not include pediatric populations.

Conclusions

Restless legs syndrome affects approximately 3% of adults and can have substantial negative effects on sleep and quality of life. Initial management includes cessation of exacerbating medications and iron supplementation for patients with low iron indices. If medication therapy is indicated, gabapentinoids are first-line treatment.

ARTICLE INFORMATION

Accepted for Publication: November 6, 2025.

Published Online: January 21, 2026. doi:10.1001/jama.2025.23247

Conflict of Interest Disclosures: Dr Winkelman reported grants from American Regent, Baszucki Group, Merck Pharmaceuticals, National Institute on Drug Abuse, and Restless Legs Syndrome Foundation; consulting fees from Alexza Pharmaceuticals, Disc Medicine, Emalex Biosciences, Haleon, Noctrix Health, and Saluda Medical; lecture fees from Azurity Pharmaceuticals; contributor fees from UpToDate outside the submitted work; membership in the Scientific and Medical Advisory Board of the Restless Legs Syndrome Foundation; and serving as chairman for the International Restless Legs Syndrome Study Group. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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