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Restless Legs Syndrome: Neurochemistry and Therapy

David Anguizola, MD[1] Alba Garcia Aragón, MD[2] Brian Moncada, MD[2]
Diego Garcia-Borreguero, MD, PhD[2]

[1] Instituto Europeo del Sueño, Panamá, Panamá
[2] Sleep Research Institute, Madrid, Spain

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Address for correspondence Diego Garcia-Borreguero, MD, PhD, Sleep Research Institute, Calle Padre Damián 44, Madrid 28036, Spain (e-mail: dgb@iis.es).

Abstract

Restless legs syndrome (RLS) is a complex sensorimotor disorder characterized by disturbances in key neurochemical pathways, including dopaminergic, glutamatergic, and adenosinergic systems. This review provides an overview of the current knowledge on RLS, including its clinical features and diagnosis, pathophysiology, and treatment (non-pharmacological and pharmacological). We examine the association between RLS and neurological disorders, genetic predispositions, and brain iron deficiency. Emerging therapies targeting glutamate and adenosine receptors, alongside established dopamine agonists and α2δ ligands, offer promising avenues for treatment.

Keywords
- neurology
- restless legs syndrome
- sleep disorders
- periodic limb movements

Restless legs syndrome (RLS) is a common sensorimotor disorder[1] significantly affecting both quality of life and sleep.[2,3] It is characterized by an uncomfortable urge to move the legs, accompanied by uncomfortable sensations, particularly when the patient is at rest, during the evening, or at night. Symptoms improve with movement.

Despite its high prevalence,[4] RLS symptoms vary both in frequency and severity, ranging from sporadic episodes to daily symptoms that severely impact sleep, quality of life, and mood.[5] The age of onset of RLS shows a bimodal distribution, with one peak at approximately 20 years of age and a second peak 20 years later.[6] However, most patients are diagnosed between their forties and sixties.

Knowledge of RLS among physicians is limited, often leading to delays in diagnosis and treatment. Many patients find it difficult to describe their symptoms, which can further contribute to these delays, exacerbating the socioeconomic impact of the disease.[7] Effective treatment not only alleviates symptoms but also reduces cardiovascular risk,[8] highlighting the need for increased recognition and timely management.[8]

In this review, we summarize current knowledge on the epidemiology, mechanisms, pathophysiology, diagnosis, and management of RLS.

Clinical Description, Quality of Life, and Epidemiology

RLS, which has a global prevalence of 3%,[4] was first described by the English physician, Sir Thomas Willis, in 1685. However, the term "restless legs syndrome" was coined in 1945 by the Swedish neurologist, Karl-Axel Ekbom, who also provided a detailed description of the clinical features in 34 patients.[9]

Patients often describe their symptoms as restlessness, unease, tightness, or a sensation of something crawling. When asked about movement, they mention a need to stretch, an urgency to move, a feeling that the legs want to move, or a compulsion to kick.[10] Some patients have no sensations before the urge to move while up to 30% of patients experience pain. The discomfort is localized below the knees, typically involving the distal anterolateral region, and occurs deep in the legs as opposed to on the skin. Although RLS has been described in the upper limbs, the legs are always affected.[11] Movement always provides relief, but the symptoms re-emerge once rest is resumed.

Symptoms follow a circadian pattern, worsening in the evening and nighttime, with peak intensity during the early morning hours. Patients with RLS often experience insomnia

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Table 1 Essential diagnostic criteria

Criteria	Description
1. Urge to move the legs	An urge to move the legs is usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2. Symptom relief by movement	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. Symptom worsening with rest	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. Circadian pattern	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 night.
5. Exclusion of other conditions	The occurrences of the above features are not solely accounted for as symptoms primary to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).
6. Specifiers for clinical course of RLS	Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year. Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.
7. Supportive clinical features	● Positive family history: Often indicative of a genetic predisposition to RLS. ● Periodic limb movements: Commonly co-occur during sleep or wakefulness. ● Response to dopaminergic treatment: Symptom improvement with dopamine agonists is a strong clinical indicator. ● Iron deficiency: Frequently associated with low serum ferritin levels (<50 μg/L), suggesting a role in pathophysiology.

Abbreviations: RLS, restless legs syndrome; WED, Willis-Ekbom disease.
This table is adapted from Allen et al[7] with permission from Elsevier.

and periodic leg movements (PLM) of sleep (PLMS; reported in at least 80% of patients with RLS) or wakefulness.

PLMS—characterized by dorsiflexion of the ankle, followed by flexion of the knee and hip during sleep—are strongly associated with RLS, but can occur independently or alongside other sleep disorders.[12] For a diagnosis of PLMS, at least four consecutive movements lasting 0.5 to 5 seconds each and separated by intervals of 4 to 90 seconds, must occur. A pathological index (more than five episodes/hour) is associated with poor sleep due to frequent microarousals and sympathetic activation during these events. While PLMS are strongly associated with RLS, they can also occur independently or alongside other sleep disorders.[12]

RLS is more common in women, and its prevalence increases with age due to its associated comorbidities or conditions: iron deficiency anemia, pregnancy, fibromyalgia, chronic kidney disease, diabetes mellitus, peripheral neuropathy (PN), lumbosacral radiculopathy, venous insufficiency, many of which increase in frequency over the age of 50.[1,13]

Certain medications/substances exacerbate symptoms. These include antihistaminergic or antidopaminergic effects (tricyclic antidepressants and typical antipsychotics), certain antidepressants (selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, except for bupropion a norepinephrine–dopamine reuptake inhibitor), lipophilic β-blockers (propranolol, bisoprolol, metoprolol, carvedilol), lithium, alcohol, and caffeine.[7]

Diagnostic Workup

The International RLS Study Group (IRLSSG)[7] has outlined essential diagnostic criteria for RLS (►**Table 1**). RLS symptom severity can be assessed using the International Restless Legs Syndrome Severity Scale (IRLS).[14]

►**Table 2A** provides an overview of the diagnostic tests that can be performed in RLS to rule out underlying. Iron studies, including a hemogram, serum iron levels, ferritin, and transferrin saturation, are particularly important. If the clinical history or neurological examination indicates potential PN, electromyography, and nerve conduction studies are recommended.[15]

Differential diagnoses for RLS include vascular disorders, tardive dyskinesias, akathisia, restlessness due to psychophysiological insomnia, calf cramps, sleep myoclonus, neuropathies, and radiculopathies.[16]

The Role of the Sleep Laboratory

Polysomnography

See ►**Table 2B** for an overview of polysomnography (PSG), commonly known as a "sleep study." In RLS, the PSG is particularly useful for the identification and quantification of involuntary limb movements during sleep, present in approximately 80 to 90% of patients with RLS. PLMS are recorded using surface electrodes placed over the tibialis anterior muscles. The frequency of PLMS correlates

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Table 2A Diagnostic tests to be performed in restless legs syndrome

Concept	Description
Basic laboratory studies	Initial evaluation to exclude underlying conditions. Includes blood count, serum iron levels, ferritin, and transferrin saturation.
Electromyography and nerve conduction studies	Recommended when the clinical history and/or neurological examination suggests a possible peripheral neuropathy.
Ferritin and transferrin in CSF	Recent studies show reduced ferritin and elevated transferrin levels in the cerebrospinal fluid of patients with RLS, whereas serum values are usually within normal ranges.
Quantitative thermal sensitivity	Potentially more sensitive tool to identify thin fiber peripheral neuropathies, even in idiopathic cases with normal results on neurological examination and conventional electrophysiological tests.
Subgroup of patients with normal evaluations	Characterized by early onset of symptoms, absence of pain, and positive family history.

Abbreviation: RLS, restless legs syndrome.

Table 2B Diagnosis using polysomnography

Concept	Description
Polysomnography	Also known as a sleep study, PSG records multiple physiological variables during sleep, including EEG, EOG, chin and leg EMG, airflow, respiratory movements, pulse oximetry, and ECG, often with video recording.
Use in RLS	PSG is useful for identifying and quantifying involuntary limb movements during sleep (PLMS), present in 80 to 90% of RLS patients. PLMS are recorded with surface electrodes on the tibialis anterior muscles.
PLMS index	The number of PLMs per hour of sleep. An index >15 is considered abnormal, with >25 classified as severe. PLMS can cause microarousals and sleep fragmentation.
Diagnostic utility	PSG is not necessary for RLS diagnosis but is helpful in atypical cases or when there is diagnostic uncertainty. It can also evaluate treatment efficacy in clinical trials.

Abbreviations: PLMS, periodic leg movements of sleep; PSG, polysomnography; RLS, restless legs syndrome.

moderately with the severity of RLS.[17] The PLMS index (defined as the number of PLMs per hour of sleep) is abnormal when above 15 PLMS per hour, and reflects a non-severe pathologic range, while any values over >25 PLMS per hour are classified as severe. PLMS may be associated with microarousals and contribute to sleep fragmentation. Although PSG is not strictly necessary to diagnose RLS, it is helpful in cases with atypical features, or any other reasons of diagnostic uncertainty.

PLMS are not specific to RLS and can occur in asymptomatic individuals, particularly the elderly, as well as in other sleep disorders such as sleep apnea or narcolepsy. While a PLMS index above 15 movements per hour of sleep is generally considered abnormal, some RLS patients may have a normal PLMS index. This variability underscores that PSG is neither necessary nor sufficient for diagnosing RLS. Instead, PSG serves as a complementary tool, particularly in atypical cases or clinical trials evaluating treatment efficacy, such as dopamine agonists and $\alpha 2\delta$ ligands.[18]

Suggested Immobilization Test

The Suggested Immobilization Test (SIT) is an objective diagnostic tool used to assess motor and sensory symptoms of RLS during wakefulness while at rest. This diagnostic test unmasks symptoms by requiring the patient to remain immobile and preventing symptom alleviation through movement. This increases its diagnostic accuracy compared with other evaluations.[19]

In the traditional SIT, the patient reclines for 60 minutes, with extended legs and an elevated trunk (45–90 degrees). The patient remains awake and avoids distracting activities. Electromyographic activity in the anterior tibial muscles is continuously recorded to detect motor dysfunctions, while symptom intensity is assessed every 10 minutes using a 10 cm visual analog scale[20] (►**Fig. 1**).

The SIT is typically performed in the evening, approximately 90 minutes before the patient's usual bedtime, when symptoms peak. However, it can also be conducted at other times critical to the patient's experience of symptoms. Its simplicity and ability to evaluate wakeful symptoms make it a valuable diagnostic tool. Its sensitivity may be reduced if performed outside the symptomatic window, potentially leading to false negatives. Combining the SIT with a PSG can provide a more comprehensive evaluation, mitigating this limitation.[20]

Multiple Suggested Immobilization Test

The Multiple Suggested Immobilization Test (mSIT) is a highly reliable and valid diagnostic tool for confirming RLS. Building on the principles of the SIT, the mSIT overcomes its limitations by incorporating multiple evaluations to improve diagnostic accuracy. It consists of four 1-hour sessions

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Fig. 1 Photo of a patient undergoing a suggested immobilization test (SIT).

spaced 1 hour apart, typically conducted throughout the afternoon. This repeated testing increases the likelihood of symptom detection across different time points and provides a more accurate assessment of daytime symptom intensity, making it the test of choice for complex or challenging clinical cases.[21]

A distinguishing feature of the mSIT is that individuals are allowed to move as much as needed as long as they are experiencing symptoms and only move to alleviate discomfort. These movements are recorded as an objective and measurable component of motor restlessness. This adaptation substantially improves the diagnostic utility of the mSIT, achieving sensitivity and specificity rates greater than 90%.[21]

Although initially designed for clinical research purposes, the mSIT's application in everyday clinical practice is mainly limited by the time required to complete the test. This limitation is mitigated by the fact that it does not need to be followed by a sleep study, simplifying its implementation in certain contexts.

Actimetry

Actimetry records a patient's voluntary and involuntary movements during daily activities using a wearable device designed to store the collected data. Such movements include tremors, postural changes during sleep, and PLMs. The latter is calculated by means of specific algorithms based on information on frequency, magnitude, etc. obtained by means of accelerometers. In general, common accelerometers vary in their sensitivity and specificity in detecting PLMS, which is likely related to the technical specifications of a given device. In the case of RLS, actigraphy facilitates an ambulatory evaluation of PLMs over extended periods, typically lasting up to a week. To perform this recording, the device is usually placed on the ankle. PLMs are recorded without knowing if the patient is awake or asleep.[22]

Combining actigraphy data with a sleep diary enhances the analysis of the collected information. The main advantages of this tool are its low cost and its ability to monitor symptoms over several days, making it a viable option as a screening tool in the primary care setting.

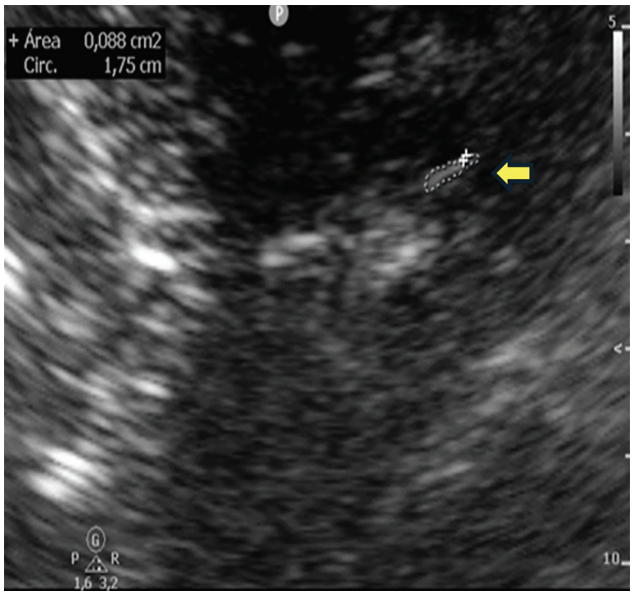

Fig. 2 Two-dimensional image obtained by means of transcranial ultrasound. A hypoechogenic substantia nigra is delineated to the left of the arrow.

Transcranial Ultrasound

Transcranial ultrasound is a non-invasive neuroimaging technique used to evaluate deep structures of the central nervous system, such as the substantia nigra. This region, which derives its name from the dark pigmentation caused by iron deposits, plays a crucial role in motor regulation and neurodegenerative pathologies. Alterations in iron concentration in this area are associated with various neurological diseases, including RLS,[22] where reduced iron deposits have been identified in this region. Transcranial ultrasound shows hypoechogenicity of the substantia nigra,[23] accompanied by preserved visualization of the red nucleus and dorsal raphe nuclei[24] (►**Fig. 2**). A hypoechogenic substantia nigra predicts a therapeutic response to intravenous iron.[25]

Restless Leg Syndrome in Neurological Disorders

Parkinson's Disease

RLS is associated with other neurological disorders, most notably, Parkinson's disease (PD). A meta-analysis of 46 studies revealed that the prevalence of RLS in individuals with PD far exceeds that of the general population (3%), with RLS affecting approximately 20% of PD patients.[26] Patients with both RLS and PD experience greater disability, affecting motor and non-motor functions, including cognitive, autonomic, and neuropsychiatric domains. Interestingly, the occurrence of RLS is not correlated with patient age or PD stage but is associated with the mixed PD phenotype (tremor with rigidity and bradykinesia) and the presence of REM sleep behavior disorder (OR 1.26, $p = 0.004$). Failures in adrenergic mechanisms may explain the relationship between RLS and PD.

Detecting and treating RLS in PD patients is essential, as the condition exacerbates anxiety, reduces quality of life, and negatively impacts nutritional status. Treatment options

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include dopamine agonists administered before bedtime, α2δ calcium channel ligands, or opioids, tailored to the severity of symptoms and individual patient needs. Careful medication selection is important because some drugs can exacerbate RLS symptoms in this population.

Other Movement Disorders

RLS has been linked to many movement disorders: RLS affects 16.9% of patients with multiple system atrophy, 33% of patients with essential tremor, 31% of patients with Wilson's disease (over 50% of whom have severe RLS symptoms), 10% of patients with Tourette's syndrome, and 32% of patients with Friedreich's ataxia. Evidence regarding RLS in other movement disorders is limited and originates mainly from case series.[27]

Peripheral Neuropathy

The absence of standardized criteria for diagnosing RLS in PN complicates prevalence estimates, with reported rates of RLS in PN ranging from 5 to 53%,[28] and PN in RLS, from 0 to 87%.[29]

The challenge in clinical practice is that both conditions manifest as leg discomfort and pain relieved by movement. However, PN symptoms typically involve well-defined paresthesias and surface-level "needle-like" pain, whereas RLS discomfort is described as internal, deeper within the limbs, and often more difficult for patients to describe. Further adding to the complexity, axonal abnormalities have been observed in patients with RLS through biopsies, nerve conduction studies, and quantitative sudomotor axonal reflex tests.[30]

Treatment response helps with differentiation: RLS symptoms improve with dopaminergic agonists and α2δ ligands, whereas PN typically responds only to the latter.[28–30] Future studies should incorporate dopaminergic agonist responsiveness, SIT, PSG, and even transcranial ultrasound as part of the inclusion criteria for RLS in the context of PN. This approach may refine diagnostic accuracy and improve the reliability of prevalence estimates.

Another condition that requires differentiation from RLS is painful legs and moving toes (PLMT), a movement disorder often associated with radiculopathy or neuropathy. PLMT has an adult-onset and is a rare disorder characterized by pain, typically of a neuropathic nature, in the feet or legs. It is associated with writhing movements of one or more toes. It is the pain that usually brings the patient to medical attention. The syndrome may be unilateral or bilateral. In contrast to RLS, PLMT does not include an urge to move legs and does not improve with motion.

Spinal Cord Disorders

RLS has also been associated with spinal cord pathologies, with one study reporting that 11.5% of patients met RLS criteria, with most cases involving lumbar spinal segment pathology, particularly lumbar spinal stenosis.[31]

However, caution is warranted when attributing the patient's discomfort and movements solely to RLS.[32] A study investigating patients with lumbar radiculopathy who met clinical RLS criteria found that symptoms resistant to conservative treatment improved significantly following surgical intervention. These findings emphasize the importance of considering alternative explanations for RLS-like symptoms and underscore the need for thorough diagnostic evaluations, particularly in patients with overlapping conditions.

Stroke

RLS can develop after an acute cerebrovascular event (stroke). A systematic review described RLS occurring after brainstem strokes, most commonly involving the anteromedial pontine region. The lesion's laterality can affect the contralateral or ipsilateral leg, or even both legs.[33] Most patients responded well to treatment, with symptoms resolving in approximately 3 months.

Other

Although not clearly linked to focal lesions, RLS has been reported with significant prevalence in multiple sclerosis and epilepsy. In MS, the prevalence of RLS is 28%. In epilepsy, the risk of developing RLS was found to be twice as high compared with controls (OR = 2.09), with a higher prevalence reported in America (35%) than in Asia (13%). These associations highlight the importance of recognizing and managing RLS in the context of other neurological disorders to improve patient outcomes.

Pathophysiology of Restless Leg Syndrome

RLS is no longer categorized as primary and secondary; it is now understood to be influenced by several factors including genetics, environment, and associated comorbidities.[34] Several disease mechanisms play a major role in pathophysiology and have become targets for therapeutic action (►**Fig. 3**).

Genetics and Genome-wide Association Studies

RLS is a highly hereditable condition, with over 60% of patients having one first-degree relative affected.[35] Genome-wide association studies (GWASs) have identified several risk polymorphisms linked to RLS, including *BTBD9, MEIS1, PTPRD, MAP2K5/SKOR1, or TOX3/BC034767*. A recent meta-analysis of GWASs involving 116,647 individuals with RLS and 1,546,466 controls of European ancestry expanded the number of risk loci to 164, including 3 on the X chromosome.

Interestingly, sex-specific meta-analyses show overlapping genetic predispositions in both sexes. Locus annotation highlights druggable genes such as glutamate receptors 1 and 4. Using a machine learning approach, the combined 5-year predictive power of these genes to identify people at risk of RLS is 87 to 91%.

MEIS1 is a transcription factor that plays an important role in the development of several organs, including central and peripheral nervous systems. Moreover, it plays a role in the ganglionic eminences of the developing forebrain,[36] and rare variants contribute to disease risk. The presence of some of these variants, first identified in RLS families and later found using targeted sequencing in additional cases of RLS, is sufficient to suppress *MEIS1* function in neural development,

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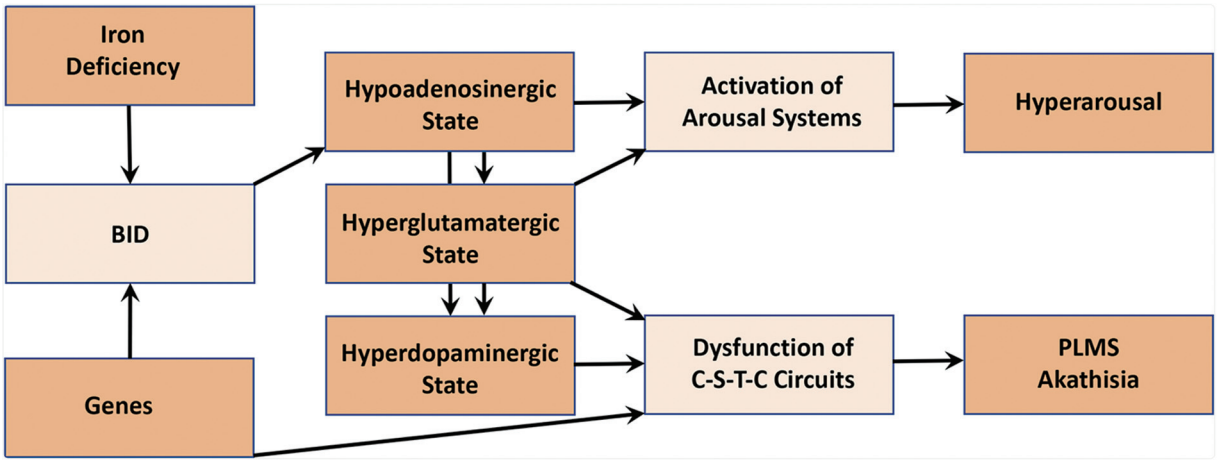

Fig. 3 Proposed integrated pathophysiological model of RLS.[110] Copyright ©2019 by Sage. Reproduced with permission of Sage Publications. BID, brain iron deficiency; PLMS, and periodic leg movements of sleep.

providing further evidence of the importance of neurodevelopmental processes in the pathological mechanism of *MEIS1* in RLS. For example, the inactivation of heterozygous *MEIS1* in mice leads to hyperactivity at the onset of the inactive period, similar to the clinical symptoms of RLS. Moreover, *MEIS1* affects the dopaminergic system at both the spinal and supraspinal levels.[37] *MEIS1* also directly regulates other RLS-related genes, including *NTNG1*, *MDGA1*, and *DACH1*.

BTBD9 has been implicated in both increased PLMS (independent of RLS) and decreased peripheral iron stores.

Brain Iron Deficiency

The prevalence of RLS symptoms in individuals with iron deficiency is four to six times higher than in the general population.[38] Most patients with RLS have brain iron deficiency (BID) but not systemic iron deficiency. Transcranial ultrasound of the substantia nigra shows that it is hypoechogenic in RLS, thereby reflecting lower levels of iron in this region.[25] RLS severity is inversely correlated with the hypoechogenicity of the SN.[39,40]

BID in RLS is also indicated by low CSF ferritin levels and (the intracellular iron storage protein) with elevated CSF transferrin levels (the extracellular iron carrier protein) despite normal serum ferritin and transferrin levels.[41] Postmortem studies show altered brain iron acquisition in RLS, characterized by changes in the expression of proteins involved in iron regulation within the choroid plexus and brain microvasculature. These include a significant reduction in intracellular iron and ferritin, along with an upregulation of transferrin receptors in RLS patients.[42]

Furthermore, alterations in transferrin receptor expression, ferritin, and the transporters DMT-1 and ferroportin suggest impaired iron transport to the brain via transferrin in RLS. BID in RLS can, therefore, result from disruptions to iron acquisition by the brain, especially through the dysregulation of iron transportation across the blood–brain barrier).[43]

Serum ferritin and transferrin saturation are the best easily available markers of peripheral iron deficiency. Other serum markers like hepcidin (regulator of iron homeostasis) are higher in RLS patients without anemia compared with controls and are associated with RLS clinical severity.[44]

Hyperdopaminergic State

Dopamine agonists provide immediate relief of RLS symptoms, highlighting the involvement of the dopaminergic system in the pathophysiology of the disorder. Initially, this clinical observation suggests diminished dopaminergic signaling. However, research shows increased dopamine synthesis and release, consistent with a presynaptic hyperdopaminergic state.[45]

Patients with RLS have reduced Fluorodopa or 6-[18] fluoro-L-DOPA uptake,[43] increased tyrosine hydroxylase (involved in dopamine synthesis staining), decreased dopamine transporter levels (involved in dopamine uptake), increased CSF biopterin (a cofactor involved in dopamine synthesis), increased CSF 3-O-Methyldopa (a metabolite of the dopamine precursor levodopa), and decreased dopamine-2 receptor (D_2R) density in the morning, with a mild increase in the afternoon.[46]

Interestingly, BID in rodents produces a similar dopaminergic profile, including, decreased striatal D_2R density, decreased DAT, and increased expression of phosphorylated TH.[46,47] Therefore, the mechanism of action of dopaminergic medications in RLS seems unclear in the context of a hyperdopaminergic state. A postsynaptic downregulation of D_2Rs, potentially leading to a nighttime dopaminergic deficit, has been suggested. More compellingly, evidence shows that the dopamine receptor agonists pramipexole and ropinirole block glutamate release in both BID rats and controls. This suggests that in RLS, dopamine receptors in striatal glutamatergic terminals could be a target for these drugs.[48]

In addition to central dopaminergic mechanisms, the descending spinal dopaminergic system originating from A11 neurons in the dorsal–posterior hypothalamus might also be involved in the pathophysiology of RLS. Selective lesioning of this pathway in animal models induces RLS symptoms.[49] Furthermore, A11 region lesions in mice increase locomotor activity, which is further exacerbated by

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iron deficiency.[50] However, biopsy studies of brain tissue from six patients with idiopathic RLS found no damage to the A11 region.[51]

The dopaminergic and BID hypotheses of RLS are not mutually exclusive. BID might alter striatal dopaminergic function, as demonstrated in animal models where iron deficiency is associated with increased extracellular striatal dopamine, reduced striatal dopamine uptake, and blunted D_2R agonist enhancement of striatal dopamine uptake. Evidence from biochemical, postmortem, and imaging studies suggest that disruptions in brain iron trafficking contribute to disturbances in striatal dopamine neurotransmission in RLS.[52]

Hyperglutamatergic State

Several studies suggest altered glutamatergic neurotransmission in RLS. For example, magnetic resonance spectroscopy shows increased thalamic basal glutamate levels in patients with RLS compared with controls.[53] Moreover, therapies that increase glutamatergic function improve RLS symptoms, for example, α2δ ligands (inhibitors of presynaptic glutamate release),[54] drugs that inhibit N-Methyl-D-Aspartate (NMDA) receptors (ketamine and methadone),[55,56] or α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-glutamate receptor (perampanel).[57] Notably, drugs that inhibit glutamate receptors may be more effective in improving both sleep duration and/or quality than dopamine receptor agonists. Conversely, in PLMS, dopamine receptor agonists are associated with a modest improvement in sleep efficiency, despite the pronounced improvement in PLMS and sensory symptoms.[58,59] Interestingly, iron deficiency might lead to hypersensitivity of the glutamatergic cortico–striatal terminals in rodents.[48,60,61]

Decreased Adenosinergic Inhibition

In rodent models, BID leads to significant downregulation of adenosine A_1 receptors (A_1R) and upregulation of striatal A_2A receptors (A_2AR), enhancing the sensitivity of glutamatergic cortico–striatal terminals.[61,62] Both A_1R and A_2AR are expressed in cortico–striatal terminals where they form A_1R–A_2AR heteromers that, in low adenosine concentrations, inhibit glutamate release, and, in high adenosine concentrations, ultimately facilitate glutamate release.[63] However, because A_1R is more sensitive to extracellular adenosine than A_2AR,[61] BID induces an A_1R downregulation leading to a hypoadenosinergic state (►**Fig. 4**).

In addition to its effects on glutamate release, A_1R and A_2AR interact specifically with dopamine D_1 receptors (D_1R) and D_2R to form A_1R–D_1R and A_2AR–D_2R heteromers, respectively.[64] These provide a complex inhibitory modulation of dopamine signals and are highly expressed in the striatum (striatonigral neuron and striatopallidal neurons).[65]

Supporting the role of adenosine in RLS, two studies—one open-label and one double-blind, placebo-controlled—have demonstrated that dipyridamole, an inhibitor of adenosine reuptake transporters ENT1 and ENT2, has therapeutic effects on RLS symptoms.[66,67] Finally, the role of adenosine in the pathophysiology of RLS is supported by the fact that caffeine, an adenosine receptor antagonist, can exacerbate RLS symptoms.

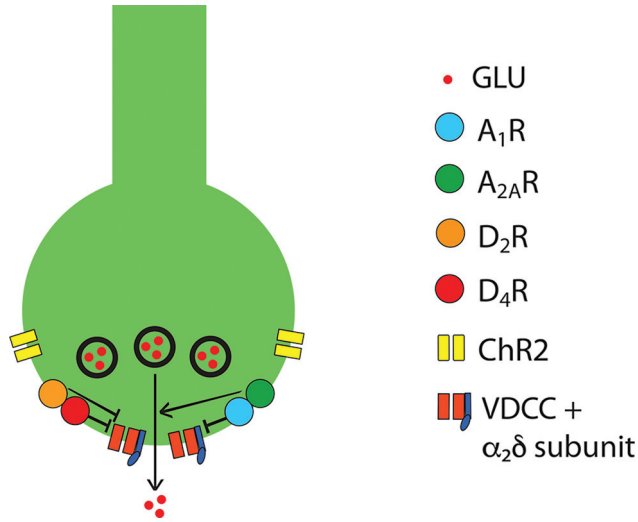

Fig. 4 The adenosine–glutamate hypothesis.[110] Copyright ©2019 by Sage. Reproduced with permission of Sage Publications. Schematic representation of a cortico–striatal glutamatergic terminal and its modulatory dopamine and adenosine receptors. Dopamine and adenosine modulate cortico–striatal glutamate (GLU) release by acting on A_1R–A_2AR and D_2R–D_4R heteromers. The A_1R–A_2AR heteromer acts as an adenosine concentration-dependent switch, by which a low adenosine concentration activates preferentially A_1R, which produces inhibition of glutamate release, and a high adenosine concentration also activates A_2AR, which shuts down A_1R signaling and promotes A_2AR-mediated stimulation of glutamate release. The D_2R–D_4R heteromer provides a dopamine concentration-dependent stepwise inhibitory mechanism of glutamate release, that depends on the higher affinity of dopamine for the D_4R and on a D_4R-mediated increase of D_2R signaling. The BID-dependent increase in the excitability of the glutamatergic terminal to release glutamate seems to depend, predominantly, on the functional downregulation of A_1R, which can be counteracted by D_2R or D_4R agonists and α2δ ligands (see text). The function of voltage-dependent calcium channels (VDCCs), whose activation promotes vesicular fusion and neurotransmitter release, is regulated by Gi-coupled receptors, including A_1R, D_2R, and D_4R, as well as by accessory α2δ subunits, the targets of gabapentin-like compounds. A_1R, adenosine A_1 receptor; A_2AR, A_2A receptor; BID, brain iron deficiency; D_1R, dopamine D_1 receptor.

Neurophysiology

Neurophysiological studies of RLS suggest it is a complex sensorimotor disorder involving dysfunctional networks at cortical, subcortical, spinal, and peripheral levels. This dysfunction results in heightened excitability, decreased inhibition, and likely impaired plasticity.[68]

Transcranial magnetic stimulation (TMS) studies show supraspinal GABA-mediated disinhibition in RLS and, conversely, suggest that a cortical origin of PLMS is unlikely.[69] Impaired inhibition is also consistent with the hyperarousal state seen in RLS patients with increased EEG high-frequency at sleep onset and increased arousal-related transient events during sleep.[70] These findings strongly suggest that reduced central inhibition contributes to the excitation state of segmental spinal pathways rather than a primary increase in excitability.

Neuroimaging

MRI studies frequently find silent cerebral microvascular disease and gliosis in patients with long-term RLS,

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potentially linking RLS with hypertension, stroke, and other cardiovascular diseases.[71] Diffusion-tensor imaging studies support these findings, showing subtle white matter changes, particularly in patients with severe symptoms. These changes are in regions involved in sensory or motor control, and sensorimotor integration, indicating possible dysfunctional integration of these networks in RLS.[72]

Decreased functional connectivity in the dopaminergic network in RLS is an expression of sensorimotor processing dysfunction involving nigrostriatal, mesolimbic, and mesocortical connections, and is accompanied by increased functional connectivity in the thalamus (ventral lateral, ventral anterior, and ventral posterior lateral nuclei, and pulvinar).[73] Multimodal MRI confirms the involvement of white matter in RLS (specifically postcentral and precentral cortex and frontopontine tract), and correlates white matter involvement with disease duration and increased gray matter volume in the right primary motor cortex (negatively correlated with the above frontopontine tract changes).

Iron content is reduced in the putamen and the temporal and occipital areas of patients with RLS. Multimodal MRI shows progressive white matter decline of somatosensory circuits, possibly supporting sensory leg discomfort. Additionally, increased gray matter volume in the premotor cortex possibly reflects functional neuronal reorganization.[74]

Resting-state functional MRI highlights distinct connectivity patterns in untreated RLS patients. Compared with controls,[75] these patients show higher intranetwork connectivity in the salience, executive, and cerebellar networks and reduced cerebello–parietal connectivity, affecting attention, response inhibitory control, and sensory processing.

Dopaminergic treatment significantly increases connectivity between the thalamus and frontal regions compared with untreated patients and controls, suggesting the therapy actively modulates thalamic function and impacts neural networks involved in RLS.

Hypoxic Pathway

Emerging evidence indicates the involvement of hypoxia in the pathophysiology of RLS. Compared with healthy controls, patients with RLS show peripheral hypoxia, measured noninvasively on the skin of the legs. Symptom severity correlates with high chest-to-foot oxygen gradient and improves with pramipexole treatment.[76]

Dopamine receptors in the vascular endothelium can cause vasodilatation and potentiate peripheral blood flow. Peripheral muscular microvascular abnormalities (i.e., capillary tortuosity) in patients with RLS are associated with lower predicted oxygen uptake.[77] Hypoxia might lead to angiogenesis with remodeling of microvascular networks, a finding supported by vascular endothelial growth factor (VEGF) upregulation in skeletal muscles of the legs in patients with RLS.[48,49,77–79]

The hypoxic pathway activates in the brains of some patients with RLS, with an upregulation of hypoxia-inducible factor (HIF)-1α in the substantia nigra.[80] Hypoxia likely increases HIF-1 expression while reducing the expression of iron-related proteins and VEGF,[46] contributing to the dysregulation observed in RLS.[81]

Management

Non-pharmacologic Management

Non-pharmacological treatments of RLS, an important part of the overall therapeutic strategy, can serve as initial treatments or complementary to pharmacological interventions. Controlled studies are lacking, resulting in many recommendations being made without a solid scientific basis[82] (see ►**Table 3**).

In mild RLS, non-pharmacological interventions can potentially eliminate the need for medication, and in moderate to severe cases, they may help reduce the required medication dosage. Strategies such as cognitive stimulation and avoiding substances like caffeine and alcohol can be effective, although the precise mechanisms underlying these benefits remain unclear.[83] (See ►**Table 4** for an overview of lifestyle changes.)

Since RLS often disrupts the first part of the nighttime sleep cycle, patients may benefit from adjusting their sleep schedule by going to bed and getting up later.[84] ►**Table 5** provides an overview of non-pharmacological recommendations.

Although some therapies, such as capsaicin cream, magnesium supplements, and halcyon bracelets, have been described, they cannot currently be recommended due to a lack of scientific evidence.

Table 3 Conservative treatment measures

Aspect	Description
Conservative measures	Initial approach or complementary to pharmacological interventions.
Controlled studies	Few controlled studies are available; proliferation of recommendations without rigorous scientific basis.
Lifestyle factors	● High caffeine intake: Avoid consumption before bedtime. ● Excessive alcohol use: Especially before sleep. ● Elevated stress levels. ● Shift work schedules. ● Intense physical activity: Avoid close to bedtime.
Sleep hygiene	Maintaining good sleep hygiene is crucial for managing RLS.
Recommendations	Incorporate adjustments into bedtime routines.

Abbreviation: RLS, restless legs syndrome.

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Table 4 Other lifestyle changes that might help in restless legs syndrome

Aspect	Description
Potential benefits	Non-pharmacological interventions can eliminate the need for medication in mild cases and reduce dosage for moderate or severe symptoms.
Strategies	Based on empirical observations, including cognitive stimulation and avoiding substances like caffeine and alcohol.
Mechanisms	The precise mechanisms underlying their effectiveness are not fully understood.
Bedtime habits	● A sleeping environment that is quiet, comfortable, and moderately cool. ● Use appropriate sleep clothing (such as silk pajamas or robes). ● Maintain a regular sleep pattern (going to bed and getting up at the same time every day, avoiding naps during the day). ● Associate the bed exclusively with sleep (e.g., not watching television from bed).

Table 5 Other non-pharmacological recommendations

Aspect	Description
Sleep schedule adjustment	Since RLS often affects the early part of the sleep cycle, patients can be advised to adjust their sleep schedule by going to bed and waking up later.
Hot or cold massage	Applying heat or cold to the affected limbs can relieve symptoms. Heat improves blood circulation, while cold helps reduce swelling.
Hot or cold baths	Immersing in hot or cold water can relax muscles and reduce uncomfortable sensations.
Physical activities	Walking, stretching, and moderate exercise can alleviate symptoms. Regular exercise, such as yoga and pilates, is beneficial in reducing RLS symptoms.
Relaxation exercises	Techniques like biofeedback and yoga can help reduce stress and improve sleep quality.
Mental distraction	Engaging in activities that keep the mind occupied, such as reading an interesting book, can help reduce the perception of symptoms.

Abbreviation: RLS, restless legs syndrome.

RLS significantly affects sleep quality and overall well-being, often leading to issues like depression, anxiety, and stress. Various non-pharmacological interventions, including acupuncture, cognitive behavioral therapy, yoga, exercise, sleep hygiene training, near-infrared light therapy, and vibration or massage techniques, have shown promise in reducing RLS symptoms, improving severity scores, mental health, and overall quality of life.

However, the available evidence remains inconclusive. Large-scale, randomized controlled trials are necessary to confirm the efficacy of these approaches and to provide clearer guidelines for managing RLS.[85]

Tonic Motor Activation

Tonic motor activation (TOMAC) is an increasingly used non-pharmacological treatment option for RLS as it significantly alleviates symptoms, with marked improvements in IRLS scores compared with sham treatments.[86]

The therapy works by bilaterally stimulating the peroneal nerves, mimicking the effects of voluntary leg movements to alleviate RLS symptoms. The effectiveness and safety of TOMAC make it a promising alternative for those seeking to avoid the side effects associated with traditional pharmacological therapies. TOMAC has received FDA clearance for use in the United States as a treatment for moderate to severe RLS in drug-unresponsive patients.

Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-pharmacological intervention for RLS that modulates neural activity in affected brain regions. Repetitive transcranial magnetic stimulation (r-TMS) provides mild to moderate subjective improvement in sensory symptoms and sleep quality,[87] and could potentially correct abnormalities in thalamic and cortical networks implicated in the pathophysiology of RLS.[88] Thus, r-TMS may not only improve motor symptoms but also has the potential to improve underlying neural dysfunction. However, more rigorous and focused studies are necessary to establish optimal stimulation protocols for RLS.

Pharmacological Treatment

RLS treatment can be divided into

1. Therapies intending to address potential underlying causes and symptomatic treatments, which aim to alleviate symptoms.
2. Symptomatic treatments.

Therapies Intending to Address Underlying Causes

Iron Supplementation

BID remains the most critical factor in the pathophysiology of RLS. Correcting iron deficiency—through oral or

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intravenous routes—is one of the most important therapeutic options.

In both cases, serum ferritin levels should be re-evaluated 8 weeks after initiating treatment to determine effectiveness. If needed, additional iron panels can be conducted every 8 weeks.

Intravenous Iron

Intravenous iron supplementation, such as ferric carboxymaltose, is an effective treatment for moderate to severe RLS, especially when serum ferritin is below 75 µg/L. A 2019 meta-analysis demonstrated significant improvements in IRLS scores and sleep quality following intravenous iron therapy.[89] A more recent large, controlled study has confirmed these effects.[90]

Many reviews focus on its effectiveness as a treatment for patients who cannot respond to oral iron and for those suffering from RLS exacerbated by other conditions, like hemodialysis or pregnancy.[91,92]

If intravenous iron is administered, ferric carboxymaltose (1,000 mg) is the preferred option due to its strong efficacy and safety profile. It can be administered in one or two sessions and is particularly effective for patients with ferritin levels below 300 µg/L and transferrin saturation under 45%. Alternative IV formulations, such as low-molecular-weight dextran, may be considered in situations where cost or availability is a constraint. Close monitoring is essential to manage potential adverse reactions, including rare hypersensitivity. In cases of symptom recurrence, repeat IV treatments may be necessary, highlighting the importance of individualized care plans.

Oral Iron

Although less effective than intravenous iron, oral iron is nonetheless an effective treatment for patients with mild to moderate iron deficiency. It improves RLS symptoms in patients whose ferritin levels are low at baseline, although gastrointestinal adverse effects are a frequent limitation.[92] Combining oral iron with vitamin C (100 mg) enhances absorption and results in better therapeutic outcomes.[93,94]

Oral iron supplementation should be started when serum ferritin is $\leq$75 µg/L or when transferrin saturation is $<$20%. Both parameters are strongly associated with the presence and severity of symptoms. For children, the threshold is serum ferritin $<$50 µg/L.[95]

Ferrous sulfate (325 mg) is likely the most common oral iron preparation in use, containing approximately 65 mg of elemental iron per dose. Twice daily administration, preferably 1 hour before meals to enhance absorption, raises serum ferritin levels and alleviates symptoms in appropriately selected patients with RLS.[94]

If oral iron proves ineffective, causes intolerable side effects (gastrointestinal side effects like nausea and constipation are frequent and can affect adherence), or is contraindicated—such as in cases of malabsorption or rapid iron loss—IV iron therapy may be initiated.

Magnesium and Vitamin B6

Magnesium, a vital mineral required for numerous enzymatic processes in the body, plays a key role in promoting muscle relaxation and regulating nerve impulses. Magnesium deficiency may worsen RLS symptoms by increasing neuronal excitability and disrupting neuromuscular function.

Similarly, vitamin B6 serves as a cofactor in the production of neurotransmitters like serotonin and dopamine, which are critical for sleep regulation and may help alleviate RLS symptoms.

Two-month treatment with magnesium oxide (250 mg) or vitamin B6 (40 mg) significantly improved sleep quality and reduced RLS symptoms compared with a placebo, with magnesium showing the strongest effect.[96] These supplements could, therefore, play a beneficial role in managing RLS symptoms, although additional studies are needed to validate the results before a general recommendation can be made.[96]

Symptomatic Treatments

Symptomatic treatment is used to treat clinically significant moderate to severe RLS symptoms which are present on most days. Treatment with a dopamine agonist, or an $\alpha 2\delta$ ligand that targets the $\alpha 2\delta$ subunit of the calcium channels, is used for this purpose.

Intermittent Restless Leg Syndrome

For moderate to severe symptoms that occur intermittently and do not warrant daily treatment but are still significant, levodopa or pramipexole is often used off-label due to the lack of approved treatments for such cases.

Continuous Symptomatic Treatment

Dopaminergic Drugs: Efficacy and long-term risks

The medications approved by the U.S. Food and Drug Administration (FDA) for managing RLS include pramipexole, ropinirole, and the transdermal rotigotine patch.

Dopaminergic drugs should only be used at the lowest effective dose, with recommended daily limits of pramipexole ($\leq$0.75 mg/day), ropinirole ($\leq$4 mg/day), and rotigotine ($\leq$3 mg/day,[97] see ►**Table 6**).

Consistent evidence shows that dopamine agonists are effective in relieving RLS symptoms, at least during the initial years of treatment.[98]

Nausea and vomiting, the most frequently reported side effects, tend to be dose-dependent. Excessive daytime sleepiness can occur, with some patients experiencing drowsiness that interferes with daily activities. Orthostatic hypotension, characterized by a drop in blood pressure upon standing, may result in dizziness or fainting. Peripheral edema, or swelling in the lower limbs, has also been documented. Furthermore, impulse control disorders (ICDs), although more typically linked to long-term use, can occur during the early stages of treatment.[99]

The long-term use of dopaminergic drugs for RLS carries a significant risk of augmenting symptom severity, a phenomenon known as dopaminergic augmentation. This is a medication-induced worsening of RLS symptoms typically

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Table 6 Main dopamine agonists used for treating restless legs syndrome

Drug	Maximum recommended dose	Maximum studied dose	Half-life ($t_{1/2}$)
Pramipexole	0.5 mg/day	Up to 0.75 mg/day in clinical trials	Approximately 8 to 12 hours
Ropinirole	4 mg/day	Up to 24 mg/day in other disorders (lower for RLS)	Approximately 6 hours
Rotigotine	3 mg/24 hours (transdermal patch)	Up to 4 mg/24 hours in studies	Approximately 5 to 7 hours after patch removal

Abbreviation: RLS, restless legs syndrome.

occurring after increasing the dosage and improving with a dosage reduction. Signs of augmentation include an earlier onset of symptoms during the day, a shortened duration of symptom relief compared with the start of treatment, and the spread of symptoms to other limbs.

Over an average of 8 years of pramipexole treatment, many patients experience a marked decline in its effectiveness, with 45 to 76% unable to sustain initial symptom relief. This often necessitates dosage escalation or the addition of other medications.[100]

Short-acting dopamine agonists might carry a higher risk of augmentation compared with their long-acting counterparts.[101] Rotigotine is the only approved 24-hour dopamine agonist formulation that provides sustained symptomatic control without peaks and troughs as observed with oral medications. This agent holds particular benefit for those patients with symptoms during both daytime and nighttime.[93]

Switching to a long-acting dopamine agonist formulation may be a practical approach for patients who experience augmentation with short-acting medications, especially if alternative treatments like α2δ ligands are unsuitable. However, the best preventive approach is to avoid dopaminergic agents unless necessary. If dopaminergic therapy is required, minimizing the dopaminergic load by using the lowest effective dose for the shortest duration is advised.

Ferritin also can be used as a biomarker to identify those patients at greater risk of augmentation and the need for alternative strategies: patients experiencing augmentation have significantly lower serum ferritin levels compared with non-augmented patients. Iron deficiency not only exacerbates RLS symptoms but also increases the likelihood of augmentation during dopaminergic therapy. Evidence suggests that iron supplementation may not only relieve baseline symptoms but also decrease the risk of augmentation in patients with low ferritin levels.[93,101,102]

Another important consideration with the use of dopamine agonists in RLS treatment is the risk of ICDs. Long-term therapy with dopamine agonists can trigger ICDs such as compulsive gambling, shopping, or hypersexuality, particularly in vulnerable individuals. While these behaviors are more commonly associated with PD, they are increasingly recognized as potential complications in RLS treatment, especially with prolonged use of dopaminergics.[103]

Dopaminergic therapies, while effective for motor symptoms, may increase the risk of ICDs by affecting the brain's reward pathways. Therefore, patients need to be closely monitored for early signs of ICDs during treatment. Alternative strategies, such as adjusting medication dosages, should be considered to mitigate risks.

RLS management should be a personalized approach, carefully weighing symptom control against the possibility of adverse behavioral effects.

α2δ Ligands

α2δ ligands, such as gabapentin, pregabalin, and gabapentin enacarbil, are increasingly recommended as first-line treatments for RLS due to their efficacy and lower risk of augmentation compared with dopamine agonists.[101,104]

Gabapentin enacarbil significantly reduces RLS symptoms and improves sleep quality, as shown by notable reductions in sleep fragmentation and insomnia.[105] Pregabalin and dopamine agonists have similar efficacy but the former has a lower risk of long-term augmentation.[93]

Pharmacological treatment should, therefore, be started with gabapentin (600–1,800 mg per day), pregabalin (150–300 mg per day), or gabapentin enacarbil (600–1,200 mg per day). Currently, gabapentin enacarbil is the only α2δ ligand approved for RLS, although unavailable in Europe.[101]

These types of medication are typically administered up to 2 hours before the expected onset of symptoms. Common side effects of α2δ ligands include dizziness, sedation, and weight gain, which may make it challenging to tolerate the most effective dosages. Compared with gabapentin, gabapentin enacarbil has improved gastrointestinal absorption and linear, predictable kinetics. Since α2δ ligands are primarily excreted unchanged through the kidneys, dose adjustments may be necessary for individuals with reduced renal function (e.g., lower doses for those with renal insufficiency).

Opioids

Opioids are an effective alternative second-line therapy for RLS, particularly in cases where dopamine agonists fail to provide adequate relief.

Opioids such as oxycodone–naloxone and methadone effectively treat severe refractory RLS. However, their use is limited due to the risk of dependency and other adverse effects. When prescribing opioids, it is essential to use an opioid-risk assessment tool to screen for potential abuse and ensure safe management.

Long-acting opioids have a low risk of dependence compared with short-acting opioids.[106] Prolonged-release oxycodone–naloxone is effective in reducing severe RLS

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symptoms and improves sleep quality as well as quality of life.[107]

A detailed review of opioid use for treatment-refractory RLS recommends low doses, for example, oxycodone (10–30 mg/day) and methadone (5–20 mg/day), emphasizing their safety and efficacy in this population, particularly when dopaminergic therapies fail or cause augmentation.[108] A median dose of 30 morphine milligram equivalents (MME) provides stable symptom control.[109] Such regimens are considered safe over the long-term but an individualized approach with careful monitoring and dosing to balance maximizing benefits while limiting risks, is recommended.[109]

Conclusion

Management of RLS requires a highly individualized approach prioritizing safety and long-term efficacy. While dopamine agonists are effective in selected cases, $\alpha 2\delta$ ligands are increasingly favored due to their lower risk of augmentation. Intravenous iron is a promising option for optimizing RLS treatment, together with therapies targeting glutamatergic and adenosinergic pathways.

Conflict of Interest

D.G-B. has performed consulting work for Emalex Biosciences, Synendos Therapeutics, and PsychoGenics Inc.

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References

1 Garcia-Malo C, Peralta SR, Garcia-Borreguero D. Restless legs syndrome and other common sleep-related movement disorders. Continuum (Minneap Minn) 2020;26(04):963–987
2 Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med 2010;11(09):807–815
3 Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. 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(03):237–246
4 Broström A, Alimoradi Z, Lind J, Ulander M, Lundin F, Pakpour A. Worldwide estimation of restless legs syndrome: a systematic review and meta-analysis of prevalence in the general adult population. J Sleep Res 2023;32(03):e13783
5 Para KS, Chow CA, Nalamada K, et al. Suicidal thought and behavior in individuals with restless legs syndrome. Sleep Med 2019;54:1–7
6 Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med 2000;1(01):11–19
7 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(08):860–873
8 Gao X, Ba DM, Bagai K, Liu G, Ma C, Walters AS. Treating restless legs syndrome was associated with low risk of cardiovascular disease: a cohort study with 3.4 years of follow-up. J Am Heart Assoc 2021;10(04):e018674
9 Coccagna G, Vetrugno R, Lombardi C, Provini F. Restless legs syndrome: an historical note. Sleep Med 2004;5(03):279–283
10 Kerr S, McKinon W, Bentley A. Descriptors of restless legs syndrome sensations. Sleep Med 2012;13(04):409–413
11 Ruppert E. Restless arms syndrome: prevalence, impact, and management strategies. Neuropsychiatr Dis Treat 2019;15:1737–1750
12 Hochstrasser KJ, Rogers SC, Quyyumi A, et al. Restless legs syndrome, periodic limb movements of sleep, and subclinical cardiovascular disease. Sleep Biol Rhythms 2023;22(02):259–267
13 Mansur A, Castillo PR, Rocha Cabrero F, Bokhari SRA. Restless Legs Syndrome. StatPearls; 2024
14 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(02):121–132
15 Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. J Sleep Res 2005;14(01):43–47
16 Chokroverty S. Differential diagnoses of restless legs syndrome/Willis-Ekbom disease: mimics and comorbidities. Sleep Med Clin 2015;10(03):249–262, xii
17 Garcia-Borreguero D, Larrosa O, de la Llave Y, Granizo JJ, Allen R. Correlation between rating scales and sleep laboratory measurements in restless legs syndrome. Sleep Med 2004;5(06):561–565
18 Manconi M, Garcia-Borreguero D, Schormair B, et al. Restless legs syndrome. Nat Rev Dis Primers 2021;7(01):80
19 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(02):324–329
20 De Cock VC, Bayard S, Yu H, et al. Suggested immobilization test for diagnosis of restless legs syndrome in Parkinson's disease. Mov Disord 2012;27(06):743–749
21 Garcia-Borreguero D, Kohnen R, Boothby L, Tzonova D, Larrosa O, Dunkl E. Validation of the Multiple Suggested Immobilization Test: a test for the assessment of severity of restless legs syndrome (Willis-Ekbom Disease). Sleep 2013;36(07):1101–1109
22 Berg D, Godau J, Walter U. Transcranial sonography in movement disorders. Lancet Neurol 2008;7(11):1044–1055
23 Garcia-Malo C, Novo-Ponte S, Castro-Villacañas Farzamnia A, et al. Correlation between systemic iron parameters and substantia nigra iron stores in restless legs syndrome. Sleep Med 2021;85:191–195
24 Godau J, Manz A, Wevers AK, Gaenslen A, Berg D. Sonographic substantia nigra hypoechogenicity in polyneuropathy and restless legs syndrome. Mov Disord 2009;24(01):133–137
25 Garcia-Malo C, Wanner V, Miranda C, et al. Quantitative transcranial sonography of the substantia nigra as a predictor of therapeutic response to intravenous iron therapy in restless legs syndrome. Sleep Med 2020;66:123–129
26 Maggi G, Barone A, Mastromarino C, Santangelo G, Vitale C. Prevalence and clinical profile of patients with restless legs syndrome in Parkinson's disease: a meta-analysis. Sleep Med 2024;121:275–286
27 Fereshtehnejad SM, Shafieesabet M, Shahidi GA, Delbari A, Lökk J. Restless legs syndrome in patients with Parkinson's disease: a comparative study on prevalence, clinical characteristics, quality of life and nutritional status. Acta Neurol Scand 2015;131(04):211–218
28 Alonso-Navarro H, García-Martín E, Agúndez JAG, Jiménez-Jiménez FJ. Association between restless legs syndrome and other movement disorders. Neurology 2019;92(20):948–964

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29 Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Association between restless legs syndrome and peripheral neuropathy: a systematic review and meta-analysis. Eur J Neurol 2021;28(07):2423–2442
30 Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC. Subclinical sensory neuropathy in late-onset restless legs syndrome. Neurology 2000;55(08):1115–1121
31 Terai H, Toyoda H, Hoshino M, et al. Prevalence of restless legs syndrome and its symptoms among patients with spinal disorders. J Clin Med 2021;10(21):5001
32 Kocabicak E, Terzi M, Akpinar K, Paksoy K, Cebeci I, Iyigun O. Restless leg syndrome and sleep quality in lumbar radiculopathy patients. Behav Neurol 2014;2014:245358
33 Kalampokini S, Poyiadjis S, Vavougios GD, et al. Restless legs syndrome due to brainstem stroke: a systematic review. Acta Neurol Scand 2022;146(05):440–447
34 Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: a systematic review and new concept. Neurology 2016;86(14):1336–1343
35 Rye DB. The molecular genetics of restless legs syndrome. Sleep Med Clin 2015;10(03):227–233, xii
36 Salminen AV, Lam DD, Winkelmann J. Role of MEIS1 in restless legs syndrome: from GWAS to functional studies in mice. Adv Pharmacol 2019;84:175–184
37 Salminen AV, Garrett L, Schormair B, et al;German Mouse Clinic Consortium. *Meis1*: effects on motor phenotypes and the sensorimotor system in mice. Dis Model Mech 2017;10(08):981–991
38 Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol 2013;88(04): 261–264
39 Pedroso JL, Bor-Seng-Shu E, Felicio AC, et al. Severity of restless legs syndrome is inversely correlated with echogenicity of the substantia nigra in different neurodegenerative movement disorders. a preliminary observation. J Neurol Sci 2012;319(1-2):59–62
40 Godau J, Sojer M. Transcranial sonography in restless legs syndrome. Int Rev Neurobiol 2010;90:199–215
41 Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000;54(08):1698–1700
42 Kapoor PM, Mavaddat N, Choudhury PP, et al;ABCTB Investigators kConFab/AOCS Investigators. Combined associations of a polygenic risk score and classical risk factors with breast cancer risk. J Natl Cancer Inst 2021;113(03):329–337
43 Connor JR, Ponnuru P, Wang XS, Patton SM, Allen RP, Earley CJ. Profile of altered brain iron acquisition in restless legs syndrome. Brain 2011;134(Pt 4):959–968
44 Dauvilliers Y, Chenini S, Vialaret J, et al. Association between serum hepcidin level and restless legs syndrome. Mov Disord 2018;33(04):618–627
45 Earley CJ, Uhl GR, Clemens S, Ferré S Connectome and molecular pharmacological differences in the dopaminergic system in restless legs syndrome (RLS): plastic changes and neuroadaptations that may contribute to augmentation. Sleep Med 2017; 31:71–77
46 Earley CJ, Connor J, Garcia-Borreguero D, et al. Altered brain iron homeostasis and dopaminergic function in Restless Legs Syndrome (Willis-Ekbom Disease). Sleep Med 2014;15(11): 1288–1301
47 Connor JR, Wang X-S, Allen RP, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain 2009;132:2403–2412
48 Yepes G, Guitart X, Rea W, et al. Targeting hypersensitive corticostriatal terminals in restless legs syndrome. Ann Neurol 2017;82(06):951–960
49 Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology 2006;67(01):125–130
50 Qu S, Le W, Zhang X, Xie W, Zhang A, Ondo WG. Locomotion is increased in a11-lesioned mice with iron deprivation: a possible animal model for restless legs syndrome. J Neuropathol Exp Neurol 2007;66(05):383–388
51 Earley CJ, Allen RP, Connor JR, Ferrucci L, Troncoso J. The dopaminergic neurons of the A11 system in RLS autopsy brains appear normal. Sleep Med 2009;10(10):1155–1157
52 Unger EL, Bianco LE, Jones BC, Allen RP, Earley CJ. Low brain iron effects and reversibility on striatal dopamine dynamics. Exp Neurol 2014;261:462–468
53 Allen RP, Barker PB, Horská A, Earley CJ. Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. Neurology 2013;80(22):2028–2034
54 Garcia-Borreguero D, Patrick J, DuBrava S, et al. Pregabalin versus pramipexole: effects on sleep disturbance in restless legs syndrome. Sleep 2014;37(04):635–643
55 Kapur N, Friedman R. Oral ketamine: a promising treatment for restless legs syndrome. Anesth Analg 2002;94(06):1558–1559
56 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(05): 440–444
57 Garcia-Borreguero D, Cano I, Granizo JJ. Treatment of restless legs syndrome with the selective AMPA receptor antagonist perampanel. Sleep Med 2017;34:105–108
58 Inoue Y, Hirata K, Kuroda K, et al. Efficacy and safety of pramipexole in Japanese patients with primary restless legs syndrome: a polysomnographic randomized, double-blind, placebo-controlled study. Sleep Med 2010;11(01):11–16
59 Oertel WH, Benes H, Garcia-Borreguero D, et al. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. Sleep Med 2010;11(09):848–856
60 McGahan MC, Harned J, Mukunnemkeril M, Goralska M, Fleisher L, Ferrell JB. Iron alters glutamate secretion by regulating cytosolic aconitase activity. Am J Physiol Cell Physiol 2005;288(05): C1117–C1124
61 Quiroz C, Gulyani S, Ruiqian W, et al. Adenosine receptors as markers of brain iron deficiency: implications for restless legs syndrome. Neuropharmacology 2016;111:160–168
62 Ferré S, Quiroz C, Guitart X, et al. Pivotal role of adenosine neurotransmission in restless legs syndrome. Front Neurosci 2018;11:722
63 Ciruela F, Ferré S, Casadó V, et al. Heterodimeric adenosine receptors: a device to regulate neurotransmitter release. Cell Mol Life Sci 2006;63(21):2427–2431
64 Ferré S, Bonaventura J, Zhu W, et al. Essential control of the function of the striatopallidal neuron by pre-coupled complexes of adenosine a_{2a}-dopamine D_2 receptor heterotetramers and adenylyl cyclase. Front Pharmacol 2018;9:243
65 Ferré S, Sarasola LI, Quiroz C, Ciruela F. Presynaptic adenosine receptor heteromers as key modulators of glutamatergic and dopaminergic neurotransmission in the striatum. Neuropharmacology 2023;223:109329
66 Garcia-Borreguero D, Guitart X, Garcia Malo C, Cano-Pumarega I, Granizo JJ, Ferré S Treatment of restless legs syndrome/Willis-Ekbom disease with the non-selective ENT1/ENT2 inhibitor dipyridamole: testing the adenosine hypothesis. Sleep Med 2018;45:94–97
67 Garcia-Borreguero D, Garcia-Malo C, Granizo JJ, Ferré S A randomized, placebo-controlled crossover study with dipyridamole for restless legs syndrome. Mov Disord 2021;36(10): 2387–2392

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68 Lanza G, Lanuzza B, Aricò D, et al. Impaired short-term plasticity in restless legs syndrome: a pilot rTMS study. Sleep Med 2018; 46:1–4
69 Lanza G, Ferri R. The neurophysiology of hyperarousal in restless legs syndrome: hints for a role of glutamate/GABA. Adv Pharmacol 2019;84:101–119
70 Ferri R, Manconi M, Aricò D, et al. Acute dopamine-agonist treatment in restless legs syndrome: effects on sleep architecture and NREM sleep instability. Sleep 2010;33(06):793–800
71 Walters AS, Paueksakon P, Adler CH, et al. Restless legs syndrome shows increased silent postmortem cerebral microvascular disease with gliosis. J Am Heart Assoc 2021;10(11):e019627
72 de Paiva JPQ, Magalhães SC, Moura LM, et al. Sensorimotor white matter projections and disease severity in primary Restless Legs Syndrome/Willis-Ekbom disease: a multimodal DTI analysis. Sleep Med 2020;73:106–116
73 Kocar TD, Müller HP, Kassubek J. Differential functional connectivity in thalamic and dopaminergic pathways in restless legs syndrome: a meta-analysis. Ther Adv Neurol Disord 2020; 13:1756286420941670
74 Stefani A, Mitterling T, Heidbreder A, et al. Multimodal Magnetic Resonance Imaging reveals alterations of sensorimotor circuits in restless legs syndrome. Sleep 2019;42(12):zsz171
75 Tuovinen N, Stefani A, Mitterling T, et al. Functional connectivity and topology in patients with restless legs syndrome: a case-control resting-state functional magnetic resonance imaging study. Eur J Neurol 2021;28(02):448–458
76 Salminen AV, Rimpilä V, Polo O. Pramipexole alters thermoregulation in restless legs syndrome. J Clin Sleep Med 2014;10(12): 1325–1329
77 Larsson BW, Kadi F, Ulfberg J, Aulin KP. Skeletal muscle morphology in patients with restless legs syndrome. Eur Neurol 2007;58 (03):133–137
78 Allen RP. Restless leg syndrome/Willis-Ekbom disease pathophysiology. Sleep Med Clin 2015;10(03):207–214, x
79 Wåhlin-Larsson B, Ulfberg J, Aulin KP, Kadi F. The expression of vascular endothelial growth factor in skeletal muscle of patients with sleep disorders. Muscle Nerve 2009;40(04): 556–561
80 Yeh WL, Lu DY, Lin CJ, Liou HC, Fu WM. Inhibition of hypoxia-induced increase of blood-brain barrier permeability by YC-1 through the antagonism of HIF-1α accumulation and VEGF expression. Mol Pharmacol 2007;72(02):440–449
81 Salminen AV, Rimpilä V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). Neurology 2014;82(21): 1856–1861
82 Sharon D. Nonpharmacologic management of restless legs syndrome (Willis-Ekbom disease): myths or science. Sleep Med Clin 2015;10(03):263–278, xiii
83 Silber MH, Buchfuhrer MJ, Earley CJ, Koo BB, Manconi M, Winkelman JWScientific and Medical Advisory Board of the Restless Legs Syndrome Foundation. The management of restless legs syndrome: an updated algorithm. Mayo Clin Proc 2021;96(07): 1921–1937
84 Klingelhoefer L, Cova I, Gupta S, Chaudhuri KR. A review of current treatment strategies for restless legs syndrome (Willis-Ekbom disease). Clin Med (Lond) 2014;14(05):520–524
85 Akbaş P, Yaman Sözbir Ş Non-pharmacological methods used in coping with restless leg syndrome (RLS): a systematic review. Sleep Biol Rhythms 2021;19:215–225
86 Singh H, Baker FC, Ojile J, et al. Efficacy and safety of TOMAC for treatment of medication-naïve and medication-refractory restless legs syndrome: a randomized clinical trial and meta-analysis. Sleep Med 2024;122:141–148
87 Oroz R, Kung S, Croarkin PE, Cheung J. Transcranial magnetic stimulation therapeutic applications on sleep and insomnia: a review. Sleep Sci Pract 2021;5:3
88 Park KM, Kim KT, Kang KW, et al;RLS Subcommittee of the Korean Sleep Research Society. Alterations of functional connectivity in patients with restless legs syndrome. J Clin Neurol 2022; 18(03):290–297
89 Avni T, Reich S, Lev N, Gafter-Gvili A. Iron supplementation for restless legs syndrome - a systematic review and meta-analysis. Eur J Intern Med 2019;63:34–41
90 Earley CJ, García-Borreguero D, Falone M, Winkelman JW. Clinical efficacy and safety of intravenous ferric carboxymaltose for treatment of restless legs syndrome: a multicenter, randomized, placebo-controlled clinical trial. Sleep 2024;47 (07):zsae095
91 Ferré S, Earley C, Gulyani S, Garcia-Borreguero D. In search of alternatives to dopaminergic ligands for the treatment of restless legs syndrome: iron, glutamate, and adenosine. Sleep Med 2017; 31:86–92
92 Trotti LM, Becker LA. Iron for the treatment of restless legs syndrome. Cochrane Database Syst Rev 2019;1(01):CD007834
93 Salminen AV, Winkelmann J. Restless legs syndrome and other movement disorders of sleep-treatment update. Curr Treat Options Neurol 2018;20(12):55
94 Wijemanne S, Ondo W. Restless Legs Syndrome: clinical features, diagnosis and a practical approach to management. Pract Neurol 2017;17(06):444–452
95 Allen RP, Picchietti DL, Auerbach M, et al;International Restless Legs Syndrome Study Group (IRLSSG) Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med 2018;41:27–44
96 Jadidi A, Rezaei Ashtiani A, Khanmohamadi Hezaveh A, Aghaepour SM. Therapeutic effects of magnesium and vitamin B6 in alleviating the symptoms of restless legs syndrome: a randomized controlled clinical trial. BMC Complement Med Ther 2022; 23(01):1
97 Garcia-Borreguero D, Cano-Pumarega I, Marulanda R. Management of treatment failure in restless legs syndrome (Willis-Ekbom disease). Sleep Med Rev 2018;41:50–60
98 Winkelmann J, Allen RP, Högl B, et al. Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice (Revised 2017)[§]. Mov Disord 2018;33(07):1077–1091
99 Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev 2011;2011(03):CD006009
100 Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med 2012;13(10): 1280–1285
101 Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med 2016;21:1–11
102 Li YS, Yeh WC, Hsu CY. Association of low serum ferritin levels with augmentation in patients with restless legs syndrome: a systematic review and meta-analysis. Sleep Med 2023; 112:173–180
103 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(07):675–684
104 Winkelman JW, Berkowski JA, DelRosso LM, et al. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2025;21(01):137–152
105 Trenkwalder C, Allen R, Högl B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol 2018;17(11):994–1005

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106 Trenkwalder C, Winkelmann J, Inoue Y, Paulus W. Restless legs syndrome-current therapies and management of augmentation. Nat Rev Neurol 2015;11(08):434–445
107 P LMB, e SSA,Castro-Villacañas A, Garcia-Borreguero D. Restless legs syndrome: challenges to treatment. Sleep Med Clin 2021;16 (02):269–277
108 Silber MH, Becker PM, Buchfuhrer MJ, et al;Scientific and Medical Advisory Board, Restless Legs Syndrome Foundation. The appropriate use of opioids in the treatment of refractory restless legs syndrome. Mayo Clin Proc 2018;93(01):59–67
109 Winkelman JW, Purks J, Wipper B. Baseline and 1-year longitudinal data from the National Restless Legs Syndrome Opioid Registry. Sleep 2021;44(02):zsaa183
110 Ferré S, García-Borreguero D, Allen RP, Earley CJ. New insights into the neurobiology of restless legs syndrome. Neuroscientist 2019;25(02):113–125

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