Academic Journal of Neuropsychiatry & Neuropsychology

Review

DOI: 10.51271/AJNN-0055

Restless legs syndrome: linking neuroanatomical mechanisms to clinical management

Süleyman Berkay Kuzyaka[1], Serpil Çilingiroğlu Anlı*[2]

[1]Medical Student, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye
[2]Department of Anatomy, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye

Received: 30/06/2026 ◆ Accepted: 03/08/2026 ◆ Published: 29/09/2026

Cite this article: Kuzyaka SB, Çilingiroğlu Anlı S. Restless legs syndrome: linking neuroanatomical mechanisms to clinical management. *Acad J Neuropsychiatry Neuropsychol* 2026;3(3):70-76. doi:10.51271/AJNN-0055

*Corresponding Author: Serpil Çilingiroğlu Anlı, serpilblue@gmail.com

ABSTRACT

Restless legs syndrome (RLS) is a common neurological sensorimotor disorder that can markedly disturb sleep, daytime functioning, and quality of life. Patients usually describe an urge to move the legs, often with unpleasant sensations that are hard to localize or put into words. Symptoms arise or worsen during rest, ease with movement, and tend to be most prominent in the evening or at night. Diagnosis is clinical; it depends on recognizing this pattern and considering disorders that can mimic RLS, in line with the International RLS Study Group criteria. RLS is not readily explained by a single pathway. Current evidence links the disorder to altered brain iron regulation, dopaminergic signaling, genetic susceptibility, basal ganglia circuitry, thalamocortical-somatosensory processing, and spinal sensorimotor pathways. These mechanisms provide a biological context for the sensorimotor features of the disorder. The management plan should be personalized, taking into account the symptom load, iron levels, co-morbidities, any secondary contributing factors, and other drugs that might aggravate the symptoms. Conservative measures may be sufficient for mild or intermittent symptoms, whereas persistent or disabling symptoms require tailored treatment. RLS is therefore better understood as a clinically important sensorimotor network disorder than as a simple sleep-related complaint.

Keywords: Restless legs syndrome, neural pathways, basal ganglia, somatosensory cortex, spinal cord, dopamine

INTRODUCTION

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological sensorimotor disorder in which patients experience an urge to move their legs, usually together with unpleasant sensations that appear or become worse during rest. Patients may use words such as tingling, crawling, pulling, aching, tension, or inner restlessness. Despite this variability, the clinical pattern is usually clear: symptoms worsen during inactivity, improve at least temporarily with movement, and become more prominent in the evening or at night.[1]

The burden of RLS is often underestimated. What may first seem like a minor complaint of leg discomfort can interfere with sleep initiation and sleep maintenance, leading to daytime fatigue, impaired concentration, and reduced quality of life.[2] Epidemiological studies suggest that RLS affects approximately 5-10% of the general population, although clinically significant symptoms requiring medical attention occur in a smaller proportion of individuals.[2,3]

Current evidence indicates that RLS is not simply a peripheral disorder of the legs. Rather, it appears to arise from interactions between brain iron regulation, dopaminergic neurotransmission, genetic susceptibility, basal ganglia circuits, thalamocortical sensory processing, and spinal sensorimotor pathways.[4-6] This network-based view helps explain the characteristic sensory discomfort, urge to move, circadian symptom pattern, temporary relief with movement, and frequent association with periodic limb movements during sleep.

This review brings together the historical background, epidemiology, pathophysiology, neuroanatomical mechanisms, clinical features, diagnostic approach, and current treatment strategies of RLS, with particular emphasis on the relationship between neuroanatomical mechanisms and clinical decision-making.

TERMINOLOGY AND HISTORY

Clinical observations resembling what is now known as RLS can be traced back to the 17th century. Thomas Willis described patients with marked restlessness of the limbs, particularly at night, in a clinical picture that is now regarded

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

as one of the earliest recognizable descriptions of RLS.[7] Although his terminology reflected the medical language of his time, the central features of nocturnal restlessness and disturbed sleep remain closely aligned with the modern understanding of the disorder.

The modern clinical identity of RLS was shaped mainly by Karl-Axel Ekbom in the mid-20th century. In his 1945 monograph, Ekbom outlined the symptom pattern that remains central to RLS today.[8] He described unpleasant sensations in the legs, an urge to move, relief with movement, and worsening of symptoms in the evening or at night. This careful clinical description helped separate RLS from nonspecific leg discomfort, peripheral pain syndromes, and general sleep complaints. It also supported the recognition of RLS as a distinct clinical entity.

'Restless legs syndrome' remains the most widely used term in clinical practice and research, whereas 'Willis-Ekbom disease' is also used to acknowledge both Willis's early observations and Ekbom's systematic clinical description.1 This historical development helped establish RLS as a defined neurological sensorimotor disorder rather than a nonspecific complaint of leg restlessness.[9]

DEFINITION AND DIAGNOSTIC CRITERIA

RLS is a neurological sensorimotor disorder defined by an urge to move the legs, usually accompanied by unpleasant sensations that appear or worsen during rest, improve with movement, and become more prominent in the evening or at night.[1] Patients may describe these sensations as tingling, pulling, aching, crawling, tension, or inner restlessness; however, the overall clinical pattern is often more important than the exact wording of the symptom.

No laboratory test, imaging finding, or polysomnographic marker can independently confirm the disorder. In practice, RLS is diagnosed by recognizing a characteristic symptom pattern in the patient's history. The International Restless Legs Syndrome Study Group criteria provide the main clinical framework for this assessment.[1]

The updated criteria require five key features. Patients have an urge to move their legs, often but not always accompanied by unpleasant sensations. Symptoms begin or worsen during rest or inactivity, improve partially or completely with movement, and show a clear evening or nighttime predominance. The same symptom pattern should not be more plausibly explained by another clinical condition.[1]

This last criterion deserves particular attention. Several disorders can resemble RLS, including peripheral neuropathy, nocturnal leg cramps, akathisia, positional discomfort, chronic venous insufficiency, arthritis, leg edema, and nonspecific musculoskeletal pain.[1,10] These disorders often lack the typical combination of rest-induced worsening, movement-related relief, and evening or nighttime predominance.

Clinical assessment should also document symptom severity, disease course, and the effect of RLS on sleep, daytime functioning, and quality of life.[1,2,11] This information helps determine clinical significance and treatment need, and provides a consistent framework for clinical follow-up and research.[1,10,11]

PREVALENCE, EPIDEMIOLOGY, AND RISK FACTORS

RLS is a relatively common neurological sensorimotor disorder, yet it is still easily missed in everyday clinical practice. Population-based studies suggest that RLS affects approximately 5-10% of the general population, although clinically significant symptoms requiring medical attention are less frequent, usually affecting about 2-3% of individuals.[2,3,12] Mild or occasional symptoms may not require treatment, whereas persistent symptoms that interfere with sleep, daytime functioning, or quality of life warrant clinical attention.

Prevalence estimates for RLS also vary across populations. Higher rates have generally been reported in Europe and North America, while several Asian studies have described lower rates.[2,3] These differences probably reflect a combination of genetic background, environmental influences, cultural differences in symptom reporting, and diagnostic awareness. In routine practice, RLS may remain unrecognized when patients present with insomnia, leg discomfort, fatigue, or nonspecific restlessness rather than clearly describing an urge to move.

Several demographic and clinical factors influence the expression of RLS. The disorder becomes more common with advancing age and is reported more often in female than in male.[12] It may also occur in children and adolescents, although symptoms in these age groups can be mistaken for growing pains, behavioral restlessness, attention-related problems, or nonspecific sleep disturbance.[13] Pregnancy is also a recognized period of increased vulnerability to RLS, particularly during the third trimester. Changes in iron metabolism, hormonal factors, and the increased physiological demands of late pregnancy are thought to contribute.[14] A positive family history is also common, particularly in patients with earlier symptom onset, supporting the role of inherited susceptibility.[15]

Secondary or exacerbated RLS should be considered when symptoms occur in association with iron deficiency, chronic kidney disease, neuropathy, pregnancy, or relevant medication exposure.[16,17] A medication review is particularly useful because antidopaminergic agents, some antidepressants, sedating antihistamines, and other centrally acting drugs may worsen symptoms in susceptible patients.[10] Identifying these factors is clinically relevant, as some are modifiable and may influence both evaluation and treatment planning.

ETIOLOGY AND PATHOPHYSIOLOGY

RLS has a multifactorial etiology and cannot be reduced to a single anatomical structure, neurotransmitter system, or peripheral process. Rather, current evidence supports a network-based model in which altered brain iron homeostasis, dopaminergic dysfunction, genetic susceptibility, thalamocortical sensory processing, and spinal sensorimotor mechanisms interact.[4-6,18,19] Primary RLS is often associated with familial predisposition and earlier

symptom onset, whereas secondary or exacerbated forms may occur in relation to iron deficiency, pregnancy, chronic kidney disease, neuropathy, or medication exposure.[6,14,16] These factors, they appear to converge on shared pathways, particularly iron-dependent dopaminergic regulation and altered sensorimotor network excitability.

In this model, abnormal sensory processing generates discomfort, while motor circuits respond with an urge to move. The temporary relief produced by movement suggests that motor activity can transiently modify this abnormal sensorimotor state.[1,6]

Brain Iron Homeostasis and Iron-Dopamine Interaction

Altered brain iron regulation has been one of the most consistent biological findings in RLS. This link is biologically meaningful because iron is involved in several key neural processes, including dopamine synthesis, myelination, mitochondrial function, and cellular energy metabolism. In dopaminergic neurons, iron also serves as a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine production.[4,20]

An important feature of RLS is that central iron deficiency may occur even when peripheral iron measures are not markedly abnormal. Evidence from neuropathological and neuroimaging studies points to altered brain iron handling in RLS. In the substantia nigra, impaired iron acquisition and reduced iron-related staining have been described in affected individuals.[21] Lower regional brain iron measures have been reported most consistently in the substantia nigra, with less prominent changes in the putamen.[22] This pattern is more consistent with a functional deficiency of iron within the central nervous system than with systemic iron deficiency alone.

Disturbed iron regulation may affect dopamine synthesis, receptor function, and circadian dopaminergic activity, which may contribute to evening worsening, the urge to move, and partial response to dopaminergic therapies. However, RLS should not be interpreted as a straightforward dopamine-deficiency state. Current evidence suggests a more complex disturbance involving iron-dependent modulation of dopaminergic and sensorimotor networks.[4,20]

Assessment of iron status is an important part of the evaluation of patients with clinically significant RLS, and iron replacement may reduce symptoms in selected patients. This makes iron metabolism one of the most clinically relevant mechanisms in RLS, linking biological vulnerability with diagnostic work-up and treatment planning.[17]

Dopaminergic Function and Basal Ganglia Circuits

Dopamine contributes to motor regulation and sensorimotor integration, largely through basal ganglia circuits. Within these circuits, the striatum, globus pallidus, substantia nigra, and subthalamic nucleus interact with motor and premotor cortical areas to shape movement initiation, inhibition, and control.[4]

Although treatment response does not make dopamine dysfunction the sole explanation for the disorder, the improvement seen with dopaminergic agents supports a role for dopamine-related pathways in its clinical expression.[23] Imaging studies have also reported changes in dopaminergic markers, including D2-receptor binding and striatal dopamine transporter availability.[24,25] The available evidence points instead to a more complex disturbance of dopaminergic regulation, shaped in part by brain iron metabolism and circadian variation in dopamine-related activity.[4]

Altered dopaminergic modulation within these circuits may contribute to the urge to move, difficulty remaining still, evening worsening, and temporary relief after movement. In this sense, basal ganglia dysfunction provides a link between the iron-dopamine interaction described above and the characteristic sensorimotor phenotype of RLS.[4,24]

Genetic Susceptibility and Neurodevelopmental Factors

Genetic susceptibility is an important part of the pathophysiology of restless legs syndrome, especially in patients with earlier symptom onset or a positive family history. Familial clustering has long suggested that inherited factors contribute to disease risk. However, RLS usually does not follow a simple monogenic pattern. Instead, available evidence supports a complex genetic background in which several variants contribute modestly to overall susceptibility.[26]

Genome-wide association studies have identified several loci associated with RLS, including regions near or within MEIS1, BTBD9, MAP2K5/SKOR1, and PTPRD.[15,18] These findings suggest that genetic factors may influence neural systems involved in sensory processing, motor regulation, and sensorimotor integration. Their main value is to help explain why some individuals may be biologically more vulnerable to developing RLS.[26]

Risk variants have been associated with neuronal differentiation, axonal guidance, synaptic organization, and circuit maturation. These changes may create a persistent vulnerability within central nervous system pathways, even if symptoms appear only later in life or after additional triggers such as iron deficiency, pregnancy, chronic kidney disease, neuropathy, or medication exposure.[18,27]

A 2024 genome-wide meta-analysis expanded the number of reported risk loci and linked RLS risk to biological pathways involved in neurodevelopment, neurotransmission, and neuronal connectivity.[27] These findings support the broader concept of RLS as a distributed sensorimotor network disorder rather than a disease of a single anatomical structure or one neurotransmitter system.

From a clinical perspective, genetic information is most useful for recognizing disease patterns rather than for routine genetic testing. A positive family history, early symptom onset, and similar complaints across generations may support the diagnosis and help distinguish primary RLS from symptoms mainly related to secondary conditions.

Thalamocortical and Somatosensory Network Involvement

The sensory component of RLS suggests that the disorder involves more than abnormal motor control. Many patients describe their symptoms as deep, unpleasant, and difficult to localize, which points toward altered central sensory

processing rather than a purely peripheral source of discomfort.[1,28] Thalamocortical and somatosensory networks are therefore relevant because they participate in the transmission, interpretation, and integration of sensory input from the lower extremities.[19,29-31]

Early imaging work identified cerebral activation patterns associated with sensory leg discomfort and periodic limb movements, including regions involved in sensorimotor processing.[19] More recent resting-state studies have emphasized altered thalamic connectivity and reduced connectivity within dopaminergic networks, supporting the view that RLS reflects distributed network dysfunction rather than a single focal abnormality.[30]

In patients with severe RLS, reduced cortical thickness has been reported in the bilateral postcentral gyrus, together with changes in corpus callosum regions connected with somatosensory pathways.[31] These findings may help explain why symptoms are experienced as deep, uncomfortable sensations closely linked to the urge to move.

Taken together, thalamocortical and somatosensory network findings provide a useful framework for understanding the sensory burden of RLS, particularly the deep and unpleasant sensations that are closely linked to motor restlessness.[19,30,31] These findings should not be interpreted as making neuroimaging a routine diagnostic tool, because RLS remains a clinical diagnosis based on established IRLSSG criteria.[1]

Spinal Sensorimotor Mechanisms and the A11 Dopaminergic System

Spinal sensorimotor mechanisms may help explain the close relationship between sensory discomfort, the urge to move, and periodic limb movements in restless legs syndrome. Sensory input from the lower limbs converges on interneuronal networks, reflex pathways, and motor neurons within the lumbosacral spinal cord. Changes in descending modulation may increase spinal excitability. This could lower the threshold for sensory discomfort and facilitate repetitive motor activity.[5,32]

The A11 dopaminergic system offers a possible anatomical link between central dopaminergic dysfunction and spinal involvement. Descending projections from the A11 region to the spinal cord are thought to influence sensory transmission, reflex activity, and motor excitability. Disturbance in this pathway may therefore contribute not only to the urge to move, but also to the motor phenomena seen in RLS.[5]

These stereotyped movements commonly involve flexion at the ankle, knee, or hip. Neurophysiological findings suggest that they may reflect state-dependent changes in spinal flexor reflex excitability.[33] Although PLMS are not specific to RLS, their frequent association with the disorder supports the view that spinal sensorimotor circuits form part of a wider network. This network includes brain iron regulation, basal ganglia circuits, thalamocortical sensory processing, and descending spinal modulation.[5,32,33]

Integrated Pathophysiological Model

RLS is best understood as a disorder of distributed sensorimotor network regulation rather than the result of a single anatomical lesion or isolated neurotransmitter abnormality. Brain iron dysregulation may influence dopamine synthesis and receptor function, while dopaminergic alterations within basal ganglia circuits may affect motor control, sensorimotor integration, and circadian symptom expression.[4,21,24] Genetic susceptibility may create a background vulnerability in these networks, which can be unmasked or worsened by factors such as iron deficiency, pregnancy, chronic kidney disease, neuropathy, or medication exposure.[18,27]

The sensory and motor features of RLS appear to arise from the interaction of supraspinal and spinal mechanisms. Altered thalamocortical and somatosensory processing may contribute to the deep, unpleasant, and difficult-to-localize sensations described by patients, whereas spinal sensorimotor excitability and A11-mediated descending modulation may help explain the urge to move and periodic limb movements during sleep.[5,19,30-33]

Altered brain iron regulation and dopaminergic transmission, together with changes in sensory processing and spinal excitability, may explain why symptoms worsen during rest, become more prominent in the evening or at night, and improve temporarily with movement. Clinically, this approach is valuable because it supports a structured evaluation of iron status, secondary contributors, aggravating medications, and treatment options tailored to the individual patient (Figure).[1,17]

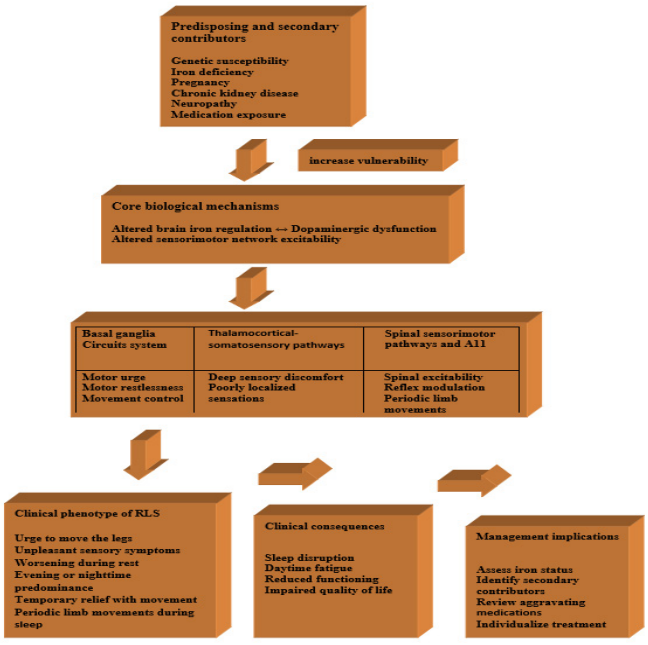


Figure. Integrated neuroanatomical and clinical model of restless legs syndrome

Genetic susceptibility and secondary contributors may interact with altered brain iron regulation, dopaminergic dysfunction, and sensorimotor network excitability. These mechanisms involve basal ganglia circuits, thalamocortical-somatosensory pathways, and spinal sensorimotor pathways, including the A11 dopaminergic system. Their interaction may explain the sensory, motor, circadian, and sleep-related features of RLS and supports individualized clinical management. RLS: Restless legs syndrome

NEUROANATOMICAL AND CLINICAL CORRELATES

The clinical manifestations of RLS are best understood as the result of altered communication within sensorimotor networks rather than dysfunction of a single anatomical structure. Although symptoms are felt mainly in the legs, the characteristic combination of sensory discomfort, urge to move, relief with movement, circadian worsening, and

periodic limb movements points to the interaction of central and spinal pathways[6,19,30,31] (Table).

Table. Neuroanatomical mechanisms and clinical correlates in RLS

Mechanism/network	Main anatomical-functional correlate	Clinical expression
Brain iron dysregulation	Substantia nigra, putamen, CNS iron handling	Dopaminergic modulation, symptom vulnerability
Dopaminergic-basal ganglia circuits	Striatum, globus pallidus, substantia nigra, subthalamic nucleus	Urge to move, motor restlessness
Thalamocortical-somatosensory processing	Thalamic networks, postcentral gyrus	Deep, unpleasant, poorly localized sensations
Spinal sensorimotor pathways	Lumbosacral spinal circuits, flexor reflex pathways	Periodic limb movements, movement-related relief
A11 dopaminergic system	Descending dopaminergic modulation	Link between central dopamine and spinal excitability

RLS: Restless legs syndrome

Basal ganglia circuits are likely to be most relevant to the motor dimension of RLS. Through striatal pathways and dopaminergic modulation, these circuits help regulate whether movement is initiated, suppressed, or adjusted in response to sensory input. In RLS, altered dopaminergic signaling within these pathways may contribute to motor restlessness and to the compelling urge to move that emerges during periods of rest.[4,24,25]

The sensory component of RLS points more strongly to thalamocortical and somatosensory processing. Patients often describe their symptoms as deep, diffuse, unpleasant, and difficult to localize, rather than as ordinary pain or numbness. Neuroimaging findings are consistent with this view, showing functional and structural changes in regions involved in sensory integration, including thalamic networks and the postcentral gyrus.[19,30,31]

Descending dopaminergic projections from the A11 system are thought to modulate spinal sensory transmission, reflex activity, and motor excitability, while state-dependent changes in spinal flexor reflex excitability may contribute to periodic limb movements during sleep.[5,33] Thus, the clinical pattern of RLS can be understood as the expression of interacting central and spinal mechanisms, although diagnosis remains based on clinical criteria rather than routine neuroimaging or neurophysiological testing.[1,6]

CLINICAL FINDINGS AND SYMPTOMATOLOGY

The clinical picture of RLS is usually built from the patient's own description. Most patients report an urge to move the legs, but the sensation that accompanies this urge is often difficult to define precisely. It may be described as pulling, tingling, crawling, tension, discomfort, or a deep inner restlessness in the legs. Although these descriptions vary, the pattern is typically consistent: symptoms appear or become worse during rest, improve for a short time with movement, and are most troublesome in the evening or at night.[1,28,29]

In some patients, symptoms remain mild and intermittent. In others, they become persistent enough to disturb sleep, limit daily activities, and make prolonged sitting or lying still difficult. Symptoms are usually bilateral and most commonly involve the calves or thighs. However, unilateral onset, asymmetry, or spread to the arms or trunk may also occur in some patients.[34]

Periodic limb movements during sleep can accompany RLS and add to sleep fragmentation. When frequent, these movements may cause repeated nocturnal awakenings, non-restorative sleep, and daytime fatigue.[34,35]

In clinically significant cases, sleep disruption, daytime fatigue, reduced concentration, and impaired quality of life may become the main reasons for seeking medical care.[2] Symptom severity can be assessed with the International RLS Rating Scale, which is useful for grading disease severity and monitoring treatment response.[11]

DIAGNOSTIC EVALUATION

RLS remains a clinical diagnosis, grounded principally in the patient's history. Ancillary tests such as laboratory studies, neuroimaging, or polysomnography may be considered when clinically indicated, but they do not establish the diagnosis in most patients. What matters is the presence of a consistent symptom pattern: an urge to move the legs that appears or worsens during rest, is relieved by movement, and is most prominent in the evening or at night. Importantly, common RLS mimics should be considered, and the diagnosis should be made only when this symptom pattern is not more plausibly explained by another clinical condition. This pattern forms the basis of the updated International Restless Legs Syndrome Study Group diagnostic criteria.[1]

Polysomnography is not routinely required. It may be helpful when the history is unclear, when periodic limb movements during sleep need objective documentation, or when another sleep disorder is suspected. Periodic limb movements are common in RLS, but they are not diagnostic on their own. For this reason, PLMS should always be interpreted together with the patient's clinical symptoms rather than used as an isolated diagnostic marker.[1,34,35]

Laboratory testing does not confirm RLS directly, but it is useful for identifying factors that may contribute to symptoms or influence management. Serum ferritin and transferrin saturation should be assessed in patients with clinically significant RLS, because iron deficiency or reduced iron availability may affect both symptom expression and treatment planning.[17]

Peripheral neuropathy, nocturnal leg cramps, akathisia, positional discomfort, chronic venous insufficiency, arthritis, leg edema, and nonspecific musculoskeletal pain may resemble RLS. In most cases, RLS can be distinguished from these mimics by its typical pattern: symptoms worsen during rest, improve with movement, and become more prominent in the evening or at night.[1,10]

MANAGEMENT AND TREATMENT

Management of RLS should be guided by the patient's overall symptom burden, including symptom frequency, severity,

sleep disruption, daytime impairment, and impact on quality of life, rather than by the diagnosis alone. Initial treatment planning should include a review of comorbid conditions, iron status, and medications that may aggravate RLS symptoms, as these factors can influence both treatment need and therapy selection.[36,37] These may include regular sleep routines, limiting prolonged inactivity when possible, reducing caffeine, alcohol, and nicotine intake, and adjusting medications that may worsen symptoms. Moderate exercise, stretching, or massage may also be considered when patients report benefit.[10,37,38]

Serum ferritin and transferrin saturation should be evaluated in patients with clinically significant RLS, because iron deficiency is a modifiable factor. In adults, iron supplementation is generally considered when ferritin is low or when transferrin saturation is reduced; intravenous iron may be appropriate in selected patients, particularly when oral iron is ineffective, poorly tolerated, or insufficient for more severe symptoms. Treatment thresholds in RLS may differ from those used for general iron deficiency.[17,36,37]

For patients requiring pharmacological treatment, alpha-2-delta ligands such as gabapentin, gabapentin enacarbil, and pregabalin are now preferred options for many adults with chronic persistent RLS, especially when sleep disturbance, pain, or prominent sensory symptoms are present.[36,37,39] Sedation, dizziness, gait instability, edema, weight gain, and renal function should be considered when selecting and dosing these agents.

Dopamine agonists, including pramipexole, ropinirole, and rotigotine, may reduce RLS symptoms in the short term, but their long-term use is limited by the risk of augmentation and impulse-control disorders.[36,40] Therefore, they should be reserved for selected patients, used at the lowest effective dose, and monitored carefully rather than presented as routine first-line long-term therapy.

Refractory RLS should prompt reassessment of the diagnosis, iron status, comorbid sleep disorders, and exacerbating medications. In selected severe cases that remain symptomatic despite standard treatment, combination therapy or low-dose opioid therapy may be considered under specialist supervision, with careful attention to adverse effects and dependence risk.[37,41]

CONCLUSION

RLS is not merely a complaint of uncomfortable legs at night. For many patients, it is a persistent sensorimotor disorder that interferes with sleep, daytime alertness, daily activities, and overall quality of life. The available evidence suggests that no single mechanism is sufficient to explain the disorder. Altered brain iron regulation, dopaminergic modulation, genetic susceptibility, basal ganglia circuitry, thalamocortical-somatosensory processing, and spinal sensorimotor excitability probably contribute to RLS in different proportions across patients. This may explain why clinical presentation varies between individuals, while the core symptom pattern remains recognizable.

Evaluation should include iron status, possible secondary causes, comorbid conditions, and medications that may worsen symptoms. Treatment should then be individualized rather than based on a single routine approach. Future studies should clarify whether different biological profiles of RLS can be identified and whether these profiles can lead to more targeted diagnostic and therapeutic strategies.

Recent publications further support this individualized approach. Diagnostic accuracy data indicate that RLS screening instruments vary in performance and should be interpreted within the full clinical context. Contemporary epidemiological and burden studies emphasize the global prevalence, regional variation, quality-of-life impact, psychiatric burden, and secondary comorbidity patterns of RLS. Updated guideline/review literature and recent intravenous ferric carboxymaltose data also support systematic assessment of iron status, secondary contributors, and careful long-term treatment selection, including cautious use of dopamine agonists because of augmentation risk.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

No financial support was received for the preparation or publication of this article.

Author Contributions

Study Design: SBK, SÇA; Conceptualization: SBK; Literature Search: SBK; Writing of the Manuscript: SBK; Critical Revision of the Manuscript: SBK, SÇA; Final Approval: SBK, SÇA; Supervision: SÇA.

Acknowledgments

The authors would like to thank Kırıkkale University Faculty of Medicine for academic support.

REFERENCES

1. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. 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(8):860-873. doi:10.1016/j.sleep.2014.03.025
2. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005;165(11):1286-1292. doi:10.1001/archinte.165.11.1286
3. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med Rev*. 2012;16(4):283-295. doi:10.1016/j.smrv.2011.05.002
4. 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. doi:10.1016/j.sleep.2014.05.009
5. Clemens S, Rye DB, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. *Neurology*. 2006;67(1):125-130. doi:10.1212/01.wnl.0000223316.53428.c9
6. Manconi M, Garcia-Borreguero D, Schormair B, et al. Restless legs syndrome. *Nat Rev Dis Primers*. 2021;7(1):80. doi:10.1038/s41572-021-00311-z
7. Willis T. De anima brutorum quae hominis vitalis ac sensitiva est. Prostant apud Gulielm. Wells & Rob. Scot; 1672.
8. Ekbom KA. Restless legs: a clinical study of a hitherto overlooked disease in the legs characterized by peculiar paresthesia. *Acta Med Scand Suppl*. 1945;158:1-123.

9. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol*. 2001;18(2):128-147. doi:10.1097/00004691-200103000-00004
10. Silber MH, Becker PM, Earley C, Garcia-Borreguero D, Ondo WG; Medical Advisory Board of the Willis-Ekbom Disease Foundation. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. *Mayo Clin Proc*. 2013;88(9):977-986. doi:10.1016/j.mayocp.2013.06.016
11. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med*. 2003;4(2):121-132. doi:10.1016/s1389-9457(02)00258-7
12. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res*. 2002;53(1):547-554. doi:10.1016/s0022-3999(02)00443-9
13. Picchietti MA, Picchietti DL. Restless legs syndrome and periodic limb movement disorder in children and adolescents. *Semin Pediatr Neurol*. 2008;15(2):91-99. doi:10.1016/j.spen.2008.03.005
14. Chen SJ, Shi L, Bao YP, et al. Prevalence of restless legs syndrome during pregnancy: a systematic review and meta-analysis. *Sleep Med Rev*. 2018;40:43-54. doi:10.1016/j.smrv.2017.10.003
15. Schormair B, Kemlink D, Roeske D, et al. PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. *Nat Genet*. 2008;40(8):946-948. doi:10.1038/ng.190
16. 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. doi:10.1212/WNL.0000000000002542
17. Allen RP, Picchietti DL, Auerbach M, et al. 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. doi:10.1016/j.sleep.2017.11.1126
18. Winkelman JW, Wipper B. Restless legs syndrome: a review. *JAMA*. 2026;335(8):703-714. doi:10.1001/jama.2025.23247
19. Bucher SF, Seelos KC, Oertel WH, Reiser M, Trenkwalder C. Cerebral generators involved in the pathogenesis of the restless legs syndrome. *Ann Neurol*. 1997;41(5):639-645. doi:10.1002/ana.410410513
20. Connor JR, Patton SM, Oexle K, Allen RP. Iron and restless legs syndrome: treatment, genetics and pathophysiology. *Sleep Med*. 2017;31:61-70. doi:10.1016/j.sleep.2016.07.028
21. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology*. 2003;61(3):304-309. doi:10.1212/01.wnl.0000078887.16593.12
22. Allen RP, Barker PB, Wehrli FW, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology*. 2001;56(2):263-265. doi:10.1212/wnl.56.2.263
23. Trenkwalder C, Hening WA, Montagna P, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord*. 2008;23(16):2267-2302. doi:10.1002/mds.22254
24. Cervenka S, Pålhagen SE, Comley RA, et al. Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. *Brain*. 2006;129(Pt 8):2017-2028. doi:10.1093/brain/awl163
25. Earley CJ, Kuwabara H, Wong DF, et al. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. *Sleep*. 2011;34(3):341-347. doi:10.1093/sleep/34.3.341
26. Schormair B. Genetics of restless legs syndrome: insights from genome-wide association studies. *Sleep Med Clin*. 2025;20(2):193-202. doi:10.1016/j.jsmc.2025.02.008
27. Schormair B, Zhao C, Bell S, et al. Genome-wide meta-analyses of restless legs syndrome yield insights into genetic architecture, disease biology and risk prediction. *Nat Genet*. 2024;56(6):1090-1099. doi:10.1038/s41588-024-01763-1
28. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord*. 1995;10(5):634-642. doi:10.1002/mds.870100517
29. Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. *Nat Rev Neurol*. 2010;6(6):337-346. doi:10.1038/nrneurol.2010.55
30. 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. doi:10.1177/1756286420941670
31. Lee BY, Kim J, Connor JR, Podskalny GD, Ryu Y, Yang QX. Involvement of the central somatosensory system in restless legs syndrome: a neuroimaging study. *Neurology*. 2018;90(21):e1834-e1841. doi:10.1212/WNL.0000000000005562
32. Dafkin C, McKinon W, Kerr S. Restless legs syndrome: clinical changes in nervous system excitability at the spinal cord level. *Sleep Med Rev*. 2019;47:9-17. doi:10.1016/j.smrv.2019.05.005
33. Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. *Neurology*. 2000;54(8):1609-1616. doi:10.1212/WNL.54.8.1609
34. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord*. 1997;12(1):61-65. doi:10.1002/mds.870120111
35. Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. *Sleep Med Rev*. 2006;10(3):169-177. doi:10.1016/j.smrv.2005.12.003
36. 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(1):137-152. doi:10.5664/jcsm.11390
37. Silber MH, Buchfuhrer MJ, Earley CJ, et al. The management of restless legs syndrome: an updated algorithm. *Mayo Clin Proc*. 2021;96(7):1921-1937. doi:10.1016/j.mayocp.2020.12.026
38. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. *J Am Board Fam Med*. 2006;19(5):487-493. doi:10.3122/jabfm.19.5.487
39. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. *N Engl J Med*. 2014;370(7):621-631. doi:10.1056/NEJMoa1303646
40. Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. *Sleep Med*. 2011;12(5):431-439. doi:10.1016/j.sleep.2011.03.003
41. Trenkwalder C, Beneš H, Grote L, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. *Lancet Neurol*. 2013;12(12):1141-1150. doi:10.1016/S1474-4422(13)70239-4