

RESTLESS LEGS SYNDROME: A LITERATURE REVIEW

**Madaeva I.M.,
Pytkina A.A.**

Scientific Centre for Family Health
and Human Reproduction Problems
(Timiryazev Str., 16, Irkutsk 664003,
Russian Federation)

Corresponding author:
Alena A. Pytkina
e-mail: alena.orlova.200@mail.ru

ABSTRACT

Restless legs syndrome (RLS) is a common sensorimotor neurological disorder that significantly disrupts sleep and is associated with an increased risk of chronic noncommunicable diseases. RLS is considered a common movement disorder, occurring approximately 50 % more frequently in women and in individuals of European descent. The etiology of the disease remains unknown. The pathophysiology of RLS is also not fully understood. Dopaminergic dysfunction is a key feature of RLS. Since its discovery, the role of iron deficiency has been emphasized, not iron levels in the peripheral blood, but rather its concentration in the central nervous system. The hyperdopaminergic state in RLS can lead to decreased endogenous opioid levels, which may contribute to impaired sensory processing. Overexpression of the estrogen signaling pathway has been confirmed in patients with RLS. RLS is characterized by an uncontrollable and distressing urge to move the legs and other body parts, often accompanied by unpleasant and irritating sensations. Symptoms often appear or worsen in the evening and at night and are relieved by voluntary movement. Currently, the diagnosis of RLS is based on the clinical picture, and therefore criteria have been developed for a more objective diagnosis. Non-pharmacological treatments include sleep hygiene, moderate-intensity exercise, yoga, leg massage, progressive compression devices for the lower extremity muscles, and avoiding factors that aggravate RLS. The development of new medications for the treatment of RLS has been somewhat delayed due to a limited understanding of its pathophysiology. Dopaminergic agonists, $\alpha 2\delta$ calcium channel ligands, and opioids are used in the treatment of RLS. The disorder is under-recognized by physicians and often remains undiagnosed. RLS is a treatable disease, but the risk of augmentation during drug therapy makes it necessary to develop effective non-drug treatment methods.

Keywords: restless legs syndrome, dopamine, $\alpha 2\delta$ calcium channel ligands, iron

Received: 30.03.2026
Accepted: 05.06.2026
Published: 23.07.2026

For citation: Madaeva I.M., Pytkina A.A. Restless legs syndrome: a literature review. *Acta biomedica scientifica*. 2026; 11(3): 79-87. doi: 10.29413/ABS.2026-11.3.10

СИНДРОМ БЕСПОКОЙНЫХ НОГ: ОБЗОР ЛИТЕРАТУРЫ

**Мадаева И.М.,
Пыткина А.А.**

ФГБНУ «Научный центр проблем
здоровья семьи и репродукции
человека» (664003, г. Иркутск,
ул. Тимирязева, 16, Россия)

Автор, ответственный за переписку:
Пыткина Алёна Андреевна
e-mail: alena.orlova.200@mail.ru

РЕЗЮМЕ

Синдром беспокойных ног (СБН) — распространенное сенсомоторное неврологическое расстройство, которое значительно нарушает сон и связан с повышенным риском хронических неинфекционных заболеваний. СБН считается распространенным двигательным расстройством, встречается примерно на 50 % чаще у женщин, а также у лиц европейского происхождения. Этиология заболевания до сих пор не установлена. Патофизиология СБН также до конца не изучена. Дофаминергическая дисфункция является ключевым признаком СБН. С самого открытия заболевания особо выделяли роль дефицита железа, но не его содержание в периферической крови, а именно концентрация в ЦНС. При СБН могут снижаться уровни эндогенных опиоидов, что может способствовать нарушению обработки сенсорных стимулов. У пациентов с СБН подтвердили избыточную экспрессию сигнального пути эстрогена. СБН характеризуется неконтролируемым и мучительным желанием двигать ногами и другими частями тела, и оно часто сопровождается неприятными и раздражающими ощущениями. Симптомы чаще появляются либо усиливаются в вечернее и ночное время, и уменьшаются при произвольных движениях. В настоящее время диагностика СБН основывается на клинической картине, в связи чем были разработаны критерии для более объективной постановки диагноза. К немедикаментозным методам лечения относятся: физические упражнения умеренной интенсивности, йога, массаж мышц ног, устройства для последовательной компрессии мышц нижних конечностей, избегание причин, усугубляющих СБН, гигиена сна. Разработка новых лекарственных препаратов для лечения СБН невозможна из-за ограниченного понимания его патофизиологии. В лечении СБН используются дофаминергические агонисты, лиганды $\alpha 2\delta$ кальциевых каналов и опиоиды. Врачи недостаточно осведомлены о данном заболевании, оно часто остается не диагностируемым. СБН является курабельным заболеванием, но риск развития аугментации на фоне лекарственной терапии делает необходимой разработку эффективных немедикаментозных методов лечения.

Ключевые слова: синдром беспокойных ног, дофамин, лиганды $\alpha 2\delta$ кальциевых каналов, железо, генетика

Статья поступила: 30.03.2026
Статья принята: 05.06.2026
Статья опубликована: 23.07.2026

Для цитирования: Мадаева И.М., Пыткина А.А. Синдром беспокойных ног: обзор литературы. *Acta biomedica scientifica*. 2026; 11(3): 79-87. doi: 10.29413/ABS.2026-11.3.10

INTRODUCTION

Restless legs syndrome (RLS) is a common sensorimotor neurological disorder characterized by discomfort in the lower extremities, occurring especially at night. People with RLS often experience an uncontrollable and distressing urge to move their legs in order to relieve the unpleasant sensation [1, 2].

It is a well-known fact that sleep disturbances are linked to an increased risk of cardiovascular diseases, diabetes mellitus, acute cerebrovascular accident, depression, and anxiety. The experience from the Irkutsk Sleep Medicine Center and the Laboratory of Somnology and Neurophysiology at the Scientific Center for Family Health and Human Reproduction Problems has convincingly shown that various sleep disorders significantly reduce quality of life and can lead to premature aging [3–5]. However, among all sleep disorders, RLS remains the least studied pathology, requiring close attention from sleep specialists, neurologists, and geriatricians.

Therefore, RLS constitutes a significant clinical concern and a public health challenge that necessitates enhanced awareness, improved diagnostic approaches, and more effective and accessible treatment modalities to mitigate its widespread impact on patients and the healthcare system.

AIM

To systematize the current data on the pathophysiology and treatment of RLS published over the past 5 years.

We conducted a review of contemporary Russian and international literature on restless legs syndrome. The following databases were used: eLibrary.ru, Scopus, PubMed, and Google Scholar. A search was performed using the keywords: restless legs syndrome, sleep, ferritin, and dopamine. Selection criteria included publication dates (2021–2026) and relevance to the subject matter of the literature review. Following a thorough verification of source credibility, 33 articles were chosen for citation in this study. Two additional articles from 2015 and 2018 were incorporated due to their practical significance in terms of treatment methods described therein.

This syndrome was first described by English physician Thomas Willis in 1685, but it was not until 1945 that Karl Ekbom defined the clinical characteristics of RLS and established it as a distinct nosological entity [6].

Epidemiology

RLS is considered the most common movement disorder, affecting up to 10 % of older adults (60–74 years old according to the World Health Organization's classification) and 20 % of those aged 80 years and over. It can also occur in children, although diagnosis in this age group can be challenging and reliable prevalence estimates cannot be reliably estimated. In adults, RLS

occurs approximately 50 % more frequently in women and in individuals of European descent [7].

Etiology

The etiology of the disease remains unknown [8]. Traditionally, RLS has been divided into primary (idiopathic) and secondary (comorbid) forms [9]. However, recent genetic data have challenged the concept of these two distinct conditions, as RLS may be independent or associated with other medical conditions. RLS may occur independently, most often at a young age, or in combination with comorbid conditions such as cardiovascular diseases, diabetes, or arterial hypertension, making accurate diagnosis challenging [10].

Genetic factors play a significant role in RLS. Twin studies and family aggregation analyses have estimated the heritability of RLS to range between 54 % and 69.4 %. Genome-wide association studies have identified risk alleles for RLS in five specific genomic regions, including MEIS1, BTBD9, PTPRD, MAP2K/SKOR1, and TOX3/BC034767, as well as in an intergenic region on chromosome 2 (rs6747972) [11]. The non-coding region of MEIS1 represents one of the strongest genetic associations, and it is part of a regulatory network involved in iron metabolism. The precise function of this protein in the biological pathway of RLS is yet to be established. This gene is highly expressed in dopaminergic neurons of the substantia nigra, which suggests a role in movement. However, its exact function in dopaminergic cells remains unknown [1].

The most common comorbid conditions that are associated with RLS include uremia, anxiety-depressive disorders, iron deficiency anemia, vitamin B12 and folic acid deficiencies, Parkinson's disease, polyneuropathy, thyroid disorders, rheumatoid arthritis, fibromyalgia, chronic venous insufficiency, and multiple sclerosis [9]. A high prevalence of RLS has been reported in patients with migraines. Pregnancy, particularly during the third trimester, is a physiological condition that is distinctly associated with the development of RLS [11]. A number of antidepressant and antipsychotic medications may potentially induce or exacerbate RLS symptoms.

Pathogenesis

The pathophysiology of RLS is not fully understood. However, several theories have been proposed. Dopaminergic dysfunction is a key feature of RLS, but it is not simply a lack of dopaminergic substances in the central nervous system (CNS) [12]. Dopamine levels in the cerebrospinal fluid (CSF) of RLS patients do not differ from those of a control group. However, a decrease in the activity of tyrosine hydroxylase, which is involved in dopamine synthesis, and its metabolites orthomethyldopamine and homovanillic acid has been observed.

Dysfunction of the locus coeruleus is associated with RLS, where hyperactivity of the noradrenergic system may contribute to motor restlessness. Stress-induced increased activity of the locus coeruleus may contribute to sleep disturbances. Furthermore, increased noradrenergic activity originating from the locus

coeruleus may exert a regulatory effect on the functional activity of dopaminergic neurons.

Single nucleotide polymorphisms in the gene that encodes dopamine- β -hydroxylase may contribute to the development of RLS by altering enzyme activity. This enzyme limits dopamine production by converting it into norepinephrine. It is expressed in noradrenergic cells in the locus coeruleus, postganglionic sympathetic fibers, chromaffin cells in the adrenal medulla, and epinephrine neurons. Dopamine- β -hydroxylase is a critical enzyme in the biosynthesis of catecholamines, which are important for neurotransmission in the adrenergic sympathetic nervous system. As a result of single nucleotide polymorphisms in the dopamine- β -hydroxylase gene, enzyme activity is altered, leading to reduced dopamine concentrations in the brain [13].

Since the discovery of the disease, particular emphasis has been placed on the significance of iron deficiency, not only in peripheral blood, but also in the CNS. It is known that iron is a co-factor for enzymes involved in the synthesis of dopamine and glutamate, and plays a role in regulating their receptors. Impaired iron transport to critical neurons can lead to subsequent local hypoxia and myelin loss [9]. Brain iron deficiency has been identified in neuropathological samples and on magnetic resonance imaging (MRI), primarily affecting the substantia nigra and to a lesser extent the putamen, caudate nucleus, and thalamus. Patients with normal serum ferritin levels have been found to have decreased ferritin levels in CSF [11]. In the cerebral vessels of RLS patients, elevated levels of hypoxia-inducible factor-1 α in neurons of the substantia nigra have been observed, as well as increased levels of hypoxia-inducible factor-1 α and vascular endothelial growth factor [12]. It is believed that the hypoxic pathway caused by iron deficiency in the brain disrupts dopamine metabolism activating an enzymatic cascade, with possible involvement of nitric oxide and adenosine. This, in turn, induces transcriptional processes that lead to increased dopamine synthesis [11].

Patients with RLS exhibit a reduction in the overall volume of the thalamus and specific thalamic nuclei, such as the inferior pulvinar, ventral posterolateral, and medial ventral nuclei. There have also been changes in the intrinsic network of the thalamus. These thalamic alterations were observed in patients who had not been treated with medication. In patients who were receiving medication, the overall thalamic volume, thalamic nuclei volumes, and intrinsic thalamic network did not differ from healthy individuals. These changes could be related to the pathophysiology of RLS, but a direct causal relationship has not yet been established.

Serum vitamin D levels were significantly lower in RLS patients compared to the control group, both in primary and secondary RLS, and were positively correlated with disease severity. However, vitamin D administration did not improve the condition of RLS patients. Expression of the vitamin D3 receptor protein has been demonstrated in midbrain dopamine neurons and their

target striatal neurons. Vitamin D enhances the expression of tyrosine hydroxylase, a rate-limiting enzyme for dopamine synthesis in brain tissue. This enzyme converts tyrosine into dopamine. The involvement of increased expression of this enzyme in RLS pathogenesis has been previously noted [14].

Although opioids have demonstrated efficacy in treating RLS, the role of the endogenous opioid system in RLS pathophysiology remains understudied [15]. Reduced levels of the endogenous opioid β -endorphin in post-mortem brain tissue from RLS patients, as well as in recent CSF studies, may provide support for the rationale behind using opioids in the treatment of RLS [16].

Excessive estrogen levels also affect dopamine and glutamate signaling. Elevated expression of the estrogen signaling pathway has been observed in patients with RLS. During the third trimester of pregnancy, estrogen levels reach their peak in the plasma, which may contribute to RLS, though the precise underlying mechanisms remain unclear [11].

Since RLS symptoms are most prominent in the evening and nighttime, the relationship between RLS and circadian rhythms has been extensively researched. Melatonin levels have been linked to worsening RLS symptoms [12]. The onset of melatonin secretion coincides with the nocturnal worsening of symptoms in RLS patients, and salivary melatonin levels peak approximately 2 hours prior to the peak intensity of sensory or motor symptoms. Furthermore, melatonin facilitates peripheral vasodilation, leading to a decrease in body temperature, which also correlates with the onset of RLS. However, the administration of exogenous melatonin significantly worsens motor symptoms in RLS patients [17]. Shift work is considered a risk factor for RLS due to forced disruption of natural circadian rhythms [15].

Reduced activity of circadian genes may lead to excessive expression of ferroptosis, causing intracellular dysregulation of iron metabolism, neuronal damage, and dopaminergic dysfunction.

These mechanisms are not independent of each other and may act synergistically: iron deficiency leads to altered dopamine synthesis and oxidative stress, which is further exacerbated by excitatory neurotransmission and immune system activation.

Clinical Features

RLS is characterized by an uncontrollable and distressing urge to move the legs and other body parts, often accompanied by uncomfortable and irritating sensations. These symptoms typically occur or worsen during the evening and night, and are relieved by voluntary movement [18]. Patients typically describe these sensations as itchiness, tightness, tension, twitches, burning, spasms, pulling, or pulsing, and less frequently as pain [8].

Although RLS primarily affects the lower extremities, it has also been reported in other body regions, such as the mouth, neck, upper limbs, face, abdomen, and genitals [12].

Patients with RLS exhibit shortened sleep, increased sleep fragmentation, and more pronounced respiratory disturbances and limb movements during sleep, compared to healthy individuals.

Pain and sleep arousal symptoms are more prevalent in women, while motor symptoms (both self-reported and detected as periodic limb movements on polysomnography) are more common among men. In contrast, women with RLS tend to experience more severe sleep disturbances and depressive moods, while men with RLS are at a higher risk for comorbid conditions such as hypertension and cardiovascular disease [19].

RLS is more prevalent in patients with other conditions, such as irritable bowel syndrome, chronic fatigue, and chronic pain in the muscles and back. Patients with RLS exhibit increased sensitivity to physical sensations and often experience high levels of anger and anxiety. Individuals with moderate to severe RLS may also experience suicidal thoughts and attempts, which is a factor that should be considered when determining the treatment plan for RLS. These factors, influencing the course of the disease, are often overlooked [20].

Sleep disturbances associated with RLS can lead to daytime consequences, such as low mood, irritability, forgetfulness, difficulty concentrating and also increase the risk of chronic non-communicable diseases [18].

The frequency and severity of RLS symptoms have direct clinical significance for treatment selection. Based on these factors, RLS can be classified into: *intermittent RLS* – symptoms that are bothersome enough to warrant treatment, but occur less than twice a week on average; *chronic RLS* – moderately or severely bothersome symptoms that occur at least twice a week and require daily treatment; *refractory RLS* – symptoms that do not respond to first-line monotherapy due to incomplete or reduced efficacy, intolerable adverse effects, or development of augmentation [12]. Augmentation refers to an iatrogenic worsening of RLS symptoms, characterized by earlier onset in the afternoon compared to before treatment, spread to the upper limbs, and shorter latency to symptom onset during rest periods.

Diagnosis

Diagnosis of RLS is typically made in primary care settings, but the variability of symptoms and their severity, including at the time of treatment initiation, make RLS a challenging condition to diagnose and treat. This can lead to under- or over-diagnosis, as some of the symptoms are nonspecific and may be indicative of other conditions.

Currently, the diagnosis of RLS is based on the clinical presentation. Therefore, in 1995, diagnostic criteria were developed to provide a more objective basis for diagnosis. These criteria were revised in 2003 and again in 2012 to improve diagnostic specificity. The most recent update, from 2012, includes the following diagnostic criteria for RLS established by the International RLS Study Group (IRLSSG) [21]:

- An urge to move the legs, which is usually accompanied by unpleasant sensations, although this is not always the case.

- Symptoms that begin or become worse during periods of rest or inactivity, such as when lying down or sitting.

- Symptoms that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

- Symptoms that occur or worsen only in the evening or at night compared to daytime.

The presence of these symptoms cannot be explained solely by other medical or behavioral conditions (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, discomfort in certain positions, habitual foot tapping).

The diagnosis of RLS can be challenging in certain age groups, particularly children and the elderly. In children, it is essential to rely on the child's own description, as they often use expressions such as "want to move" or "need to kick" to describe their urge to move their legs [11].

Imaging techniques are essential tools for diagnosing and comprehending RLS. Brain MRI has revealed a reduction in white matter volume within the corpus callosum, anterior cingulate gyrus, and precentral gyrus, suggesting structural changes such as myelin sheath degradation. MRI data also allow for the quantification of non-heme iron accumulation in the brain using sequences that are sensitive to tissue magnetic susceptibility. These data indicate decreased iron levels in the midbrain, which correlate with RLS severity [9].

Functional MRI has revealed abnormal activation in various areas of the sensorimotor and limbic systems, suggesting that these regions may play a role in the pathogenesis of RLS [22].

Polysomnography (PSG) is the gold standard for the objective assessment of sleep quantity and quality. It provides quantitative sleep parameters that allow clinicians to differentiate between sleep phases and stages. It is not mandatory for RLS diagnosis but can be useful, since detection of increased periodic limb movements during sleep is a supportive criterion for RLS. PSG can also identify significant objective sleep abnormalities, such as prolonged sleep onset latency and an increased arousal index [23]. In women with RLS, there is significantly less N1 sleep and more N3 sleep compared to men. Men are thought to have higher rates of periodic limb movements during sleep, and subsequent microarousals, followed by N1 sleep, while women have more N3 sleep. However, although women had more N3 sleep, they were less satisfied with their sleep than men, indicating that women perceive RLS symptoms as more distressing than men [24].

Laboratory tests to confirm the diagnosis of RLS are even less specific and provide insufficient information. Extensive research is ongoing to identify effective biomarkers for RLS. Twenty-four potential N-glycan biomarkers have been identified, which show significant

differences from a control group [21]. RLS and N-glycans are closely related to immunology and inflammation, but currently there is not enough evidence to support the use of N-glycans for clinical diagnosis of RLS.

Treatment

Pharmacological Methods

The development of novel drugs for RLS treatment has been slightly delayed due to a lack of complete understanding of its pathophysiology. Nevertheless, several groups of drugs with distinct modes of action have shown efficacy [16].

RLS treatment should be initiated daily when symptoms become significant, i.e., when they significantly affect quality of life. This is particularly important in chronic cases. For intermittent RLS, treatment may be given episodically [11].

Dopamine agonists have long been considered the first-line treatment for RLS, but their use is limited by adverse effects.

One of the most significant challenges in managing RLS with dopamine agonist therapy is the occurrence of a paradoxical worsening of symptoms. Patients initially respond well to dopamine agonists, but as treatment progresses, symptoms may worsen. This phenomenon, known as augmentation, was first reported by R. Allen and C. Earley in 1996 among patients treated with levodopa. Augmentation manifests itself as an increase in the severity of clinical symptoms, an earlier onset of symptoms (either during the day or in the early evening), involvement of additional body parts, and a reduction in the duration of effect of dopamine agonist medications. Augmentation may also occur with drugs from other classes, although it is less common [9]. The pathophysiology of augmentation is unclear and complex. However, it is believed that overstimulation of dopamine receptors leading to neuroplastic changes is a major contributing factor. Risk factors for augmentation therapy include long duration of disease, a history of smoking, current smoking, high levels of smoking, alexithymia, higher scores on the RLS severity scale, symptoms of impulse control disorders, and higher doses of dopamine agonist medications [25]. Despite the development of augmentation, dopamine agonist medication has been shown to be effective in managing the increases in heart rate and blood pressure that are associated with periodic limb movement disorder during sleep, a condition that can lead to cardiovascular disease. Additionally, women may experience a more acute response to dopamine agonist therapy than men, possibly due to differences in the expression of dopamine receptor genes in the CNS.

However, in order to prevent the development of this undesirable effect (augmentation), it has recently been recommended that pharmacological treatment should begin with the use of $\alpha 2\delta$ calcium channel ligands, such as pregabalin, gabapentin, and gabapentin enacarbil. These agents are considered to be as effective as dopamine agonists, but they have a significantly lower risk of causing augmentation [6]. The mechanism

of their action is believed to involve reducing glutamate release. $\alpha 2\delta$ calcium channel ligands have shown promising results in reducing hyperexcitability, hyperactivity, and improving deep sleep in RLS patients. There is evidence suggesting that the rate of visits to emergency departments or hospitalizations due to mental health issues was higher among patients who started treatment with gabapentinoids compared to those who began treatment with dopaminergic medications; however, there was no statistically significant increase in risk associated with the use of gabapentinoids [26].

Opioid analgesics can be effective in treating RLS, but they should be used with caution due to their potential risk of dependency. It is recommended to start with opioid drugs with lower potency and then gradually increase the dosage if necessary [23].

In the case of refractory RLS, a sequential monotherapy approach using different drug classes (e.g., $\alpha 2\delta$ calcium channel ligands, dopaminergic agents, opioids, etc.) should be considered. In cases where augmentation is required, it may be beneficial to reduce the dose and/or completely withdraw dopaminergic medications, although this may be difficult to achieve without the addition of "rescue" or transitional therapies using drugs from other classes, such as $\alpha 2\delta$ calcium channel ligands or opioids.

Non-Pharmacological Methods

Non-pharmacological treatment methods include: moderate-intensity physical activity, yoga, lower limb muscle massage, sequential compression devices for the lower limb muscles, peripheral peroneal nerve stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation. Additionally, it is recommended to avoid factors that may exacerbate RLS, such as alcohol, caffeine, nicotine, and certain antidepressants. Sleep hygiene should also be maintained [27–30].

Physical exercise is a promising non-pharmacological treatment for RLS, but high-intensity exercise may in some cases worsen the condition. There is variability in the individual response to exercise, with some people experiencing symptom improvement and others experiencing worsening after exercise. In studies conducted, participants noted that morning exercise generally alleviated symptoms, whereas evening physical activity tended to exacerbate them. In mild cases of RLS, people with secondary forms and those with a lower body mass index appear to find physical exercise more effective for relief [2].

Over the years, several non-invasive devices have been developed, including those that provide vibrational or compressive stimulation to the legs. However, none of these devices have yet been proven effective in a randomized, placebo-controlled trial [31].

Peripheral peroneal nerve stimulation is a non-pharmacological treatment for moderate-to-severe RLS that does not respond to drug therapy. It involves the use of a bilateral wearable device that applies high-frequency electrical stimulation to the peroneal nerve.

This stimulation activates a therapeutic mechanism, reducing discomfort during sleep and improving sleep quality. This treatment method has been shown to reduce RLS symptoms as an adjunct to other treatments or as a monotherapy [28].

Transcranial magnetic stimulation is a technique that alters cortical excitability and has been suggested as an effective treatment for conditions related to hyper- or hypo-excitability in the brain. This technique can significantly alleviate motor symptoms, sleep disturbances, and anxiety in patients with RLS [29].

Superficial application of heat and cold involves exposing the skin and underlying tissues to different temperatures in order to alter their temperature. This therapeutic method is based on superficial techniques that use conduction or convection mechanisms. The application of heat improves blood circulation by promoting the delivery of nutrients and oxygen to cells. Conversely, cold application enhances the production of white blood cells, reduces the levels of histamine, and strengthens the body's immune response. There is some evidence to suggest that this technique also has antioxidant effects and influences plasma norepinephrine levels, which may lead to increased neurotransmitter activity [32].

Massage has been shown to be beneficial for patients' well-being, both physically and psychologically. On the one hand, it can relieve tension in the skin and muscles, improving blood circulation and boosting the immune system. This, in turn, can lead to a sense of relaxation and contentment. However, despite the common use of massage therapy in patients with RLS, its effectiveness in treating this condition remains a topic of debate [33].

Patients with RLS may require iron replacement therapy, either through increased intake of iron-rich foods or initiation of oral or intravenous iron therapy, if blood ferritin levels are below 75 ng/mL or transferrin saturation is < 20 %. Moreover, studies conducted on RLS patients have shown that intravenous iron therapy is effective for RLS patients who do not have iron overload, with serum ferritin levels ranging from 100–300 µg/L. These data challenge current recommendations and suggest that intravenous iron administration could be considered for a wider range of RLS patients [15].

Several treatment strategies may need to be implemented simultaneously, including pharmacogenomic testing, strategies to improve treatment adherence, optimization of drug therapy, cognitive-behavioral therapy for insomnia, and management of concurrent chronic conditions [12].

CONCLUSION

Restless legs syndrome is a common neurological disorder that significantly affects quality of life and is a complex condition that remains inadequately understood from a therapeutic standpoint.

The significance of timely diagnosis and effective management is emphasized by studies examining the associations between RLS and somatic and psychological disorders.

At present, there are no established laboratory or instrumental diagnostic methods that can confirm a diagnosis of RLS. Diagnosis is currently based solely on clinical criteria, such as patient complaints and medical history, which may be insufficient, especially when dealing with pediatric and geriatric patients.

Due to the contraindications of most RLS medications during pregnancy and breastfeeding, further research into non-pharmacological treatments is needed.

Available pharmacological treatment options for RLS appear to be insufficient, and there is a need for further research into the pathophysiology of RLS in order to develop more effective therapies. Additionally, increased public awareness about RLS is also necessary.

Reducing RLS symptoms through medication and creating a calm sleeping environment meets psychological needs. Controlling RLS symptoms, engaging in activities, having trust in treatment, and receiving social support contribute to a high quality of life. A holistic and patient-centered approach that addresses physiological, psychological, and social aspects can help healthcare professionals provide comprehensive care for patients with RLS.

Analysis of the literature over recent years suggests that RLS is a manageable condition, but the risk of augmentation during drug therapy necessitates the development of effective non-pharmacological treatment methods.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Seeman MV. Why Are Women Prone to Restless Legs Syndrome? *Int J Environ Res Public Health*. 2020; 17(1): 368. doi: 10.3390/ijerph17010368
2. Cederberg KLJ, Sikes EM, Mignot E. Perceptions of exercise and restless legs syndrome: Results from a nationwide survey. *J Sleep Res*. 2024; 33(1): e13980. doi: 10.1111/jsr.13980
3. Madaeva I, Petrova V, Kolesnikova L, Shevyrtalova O. Obstructive sleep apnea / hypopnea syndrome and lipid peroxidation. *Pulmonology*. 2009; 2: 65–69. (In Russ.). [Мадаева И., Петрова В., Колесникова Л., Шевырталова О. Синдром обструктивного апноэ / гипопноэ сна и перекисное окисление липидов. *Пульмонология*. 2009; 2: 65–69.]. doi: 10.18093/0869-0189-2009-2-65-69
4. Madaeva IM, Titova EV, Berdina ON, Sholokhov LF, Kolesnikov SI, Kolesnikova LI. Changes the level of differentiating growth factor — GDF 15 in patients with sleep apnea syndrome after aPAP-therapy: pilot study. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2024; 124(5-2):

- 118–124. (In Russ.). [Мадаева И.М., Титова Е.В., Бердина О.Н., Шолохов Л.Ф., Колесников С.И., Колесникова Л.И. Изменение уровня дифференцировочного фактора роста — GDF 15 у пациентов с синдромом апноэ сна на фоне aPAP-терапии: пилотное исследование. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2024; 124(5-2): 118–124.]. doi: 10.17116/jnevro2024124052118
5. Madaeva IM, Titova EV, Berdina ON, Sholokhov LF, Semenova NV, Kolesnikov SI, Kolesnikova LI. GDF11 (Protein of Juvenility) and GDF15 (Protein of Senility) in the Plasma of Patients with Sleep Apnea Syndrome: a Pilot Study. *Bull Exp Biol Med*. 2024; 177(2): 274–277. doi: 10.1007/s10517-024-06172-2
6. Nanayakkara B, Di Michiel J, Yee BJ. Restless legs syndrome. *Aust J Gen Pract*. 2023; 52(9): 615–621. doi: 10.31128/AJGP-02-23-6722
7. Poplawska-Domaszewicz K, Rota S, Qamar MA, Chaudhuri KR. The complexities in the differential diagnosis of restless legs syndrome (Willis-Ekbom disease). *Expert Rev Neurother*. 2025; 25(2): 157–173. doi: 10.1080/14737175.2025.2450639
8. Alaçam Köksal S, Boncuk Ulaş S, Acar BA, Acar T, Güzey Aras Y, Köroğlu M. Evaluation of the relationship between idiopathic restless legs syndrome and serum hepcidin levels. *Brain Behav*. 2023; 13(11): e3259. doi: 10.1002/brb3.3259
9. Katunina EA, Titova NV, Katunin DA, Bagmanyany SD, Pogorova AR. Restless legs syndrome. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2021; 121(2): 106–113. (In Russ.). [Катунина Е.А., Титова Н.В., Катунин Д.А., Багманян С.Д., Погорова А.Р. Синдром беспокойных ног. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2021; 121(2): 106–113.]. doi: 10.17116/jnevro2021121021106
10. Trenkwalder C, Allen R, Högl B, Clemens S, Patton S, Schormair B, Winkelmann J. Comorbidities, treatment, and pathophysiology in restless legs syndrome. *Lancet Neurol*. 2018; 17(11): 994–1005. doi: 10.1016/S1474-4422(18)30311-9
11. Didato G, Di Giacomo R, Rosa GJ, Dominese A, de Curtis M, Lanteri P. Restless Legs Syndrome across the Lifespan: Symptoms, Pathophysiology, Management and Daily Life Impact of the Different Patterns of Disease Presentation. *Int J Environ Res Public Health*. 2020; 17(10): 3658. doi: 10.3390/ijerph17103658
12. Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless Legs Syndrome: Contemporary Diagnosis and Treatment. *Neurotherapeutics*. 2021; 18(1): 140–155. doi: 10.1007/s13311-021-01019-4
13. Algül FE, Tatli S, Yesilada E. Associations Between Dopamine Beta-Hydroxylase Gene Polymorphisms and Restless Legs Syndrome: A Case-Control Study. *Med Sci Monit*. 2025; 31: e947267. doi: 10.12659/MSM.947267
14. Xu XM, Ruan JH, Tao T, Xiang SL, Meng RL, Chen X. Role of vitamins in the pathogenesis and treatment of restless leg syndrome: A systematic review and meta-analysis. *PLoS One*. 2025; 20(3): e0313571. doi: 10.1371/journal.pone.0313571
15. Garcia-Malo C, Cano-Pumarega I, Castro-Villa-cañas-Farzamnia A, Boi S. Circadian Pattern in Restless Legs Syndrome: Implications for Treatment Posology. *Sleep Sci*. 2024; 17(4): e470-e475. doi: 10.1055/s-0044-1782176
16. Winkelman JW, Berkowski JA, DelRosso LM, Koo BB, Scharf MT, Sharon D, et al. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2025; 21(1): 153–199. doi: 10.5664/jcsm.11392
17. Leite EDM, Maximiano-Barreto MA, Lambert L, Werceles VO, Éckeli ÁL, Chagas MHN. Restless legs syndrome and ferritin levels in older adults with dementia: a cross-sectional study. *Dement Neuropsychol*. 2025; 19: e20240218. doi: 10.1590/1980-5764-DN-2024-0218
18. Buchfuhrer MJ, Baker FC, Singh H, Kolotovska V, Adlou B, Anand H, et al. Noninvasive neuromodulation reduces symptoms of restless legs syndrome. *J Clin Sleep Med*. 2021; 17(8): 1685–1694. doi: 10.5664/jcsm.9404
19. Kim J, Kim JR, Park HR, Joo EY. Sex-specific patterns of discomfort in patients with restless legs syndrome. *J Clin Sleep Med*. 2024; 20(2): 253–259. doi: 10.5664/jcsm.10848
20. Alkaş D, Yaman GB, Ünlü MD, Işcan G, Eren İ. Alexithymia, Anger, Sensitivity to Mild Bodily Sensations and Personality Characteristics of Restless Legs Syndrome Patients: A Case-control Study. *Türk Psikiyatri Derg*. 2024; 35(4): 271–281. doi: 10.5080/u27472
21. Odzakovic E, Allgurin M, Jonasson LL, Öberg S, Fridlund B, Ulander M, et al. Experiences of facilitators and barriers for fulfilment of human needs when living with restless legs syndrome: a qualitative study. *Int J Qual Stud Health Well-being*. 2024; 19(1): 2348884. doi: 10.1080/17482631.2024.2348884
22. Li C, Sun W, Xu L, Chen C, Fang L, Tang Yet, et al. Cerebral blood flow changes in maintenance hemodialysis patients with restless legs syndrome and their clinical significance: a cross-sectional case-control study. *BMC Neurol*. 2024; 24(1): 128. doi: 10.1186/s12883-024-03636-w
23. Mathur A, Bhat A, Gohar A. Restless Legs Syndrome in Adult Primary Care. *Cureus*. 2025; 17(8): e90090. doi: 10.7759/cureus.90090
24. Holzknecht E, Hochleitner M, Wenning GK, Högl B, Stefani A. Gender differences in clinical, laboratory and polysomnographic features of restless legs syndrome. *J Sleep Res*. 2020; 29(3): e12875. doi: 10.1111/jsr.12875
25. Heim B, Ellmerer P, Stefani A, Bergmann M, Brandauer E, Seppi K, et al. Factors associated with augmentation in patients with restless legs syndrome. *Eur J Neurol*. 2022; 29(4): 1227–1231. doi: 10.1111/ene.15221
26. Costales B, Vouri SM, Brown JD, Setlow B, Goodin AJ. Incident mental health episodes after initiation of gabapentinoids vs. dopamine agonists for early-onset idiopathic restless legs syndrome. *Psychiatry Res*. 2023; 328: 115479. doi: 10.1016/j.psychres.2023.115479

27. Ratnani G, Harjpal P. Advancements in Restless Leg Syndrome Management: A Review of Physiotherapeutic Modalities and Their Efficacy. *Cureus*. 2023; 15(10): e46779. doi: 10.7759/cureus.46779
28. Berkowski AJ, Koo BB. Can tonic motor activation be the magical elixir for restless legs syndrome? *Sleep*. 2023; 46(10): zsad230. doi: 10.1093/sleep/zsad230
29. Mohammadi MM, Ahmadi M, Vaisi Raygani AA. The Effect of Superficial Heat-Cold Application on the Sleep Quality of Patients with Restless Leg Syndrome: A Systematic Review and Meta-Analysis. *Nurs Open*. 2024; 11(11): e70080. doi: 10.1002/nop2.70080
30. Karroum EG, Bachmann CG, Bronstone A, Morrison L. Efficacy and safety of tonic motor activation (TO-MAC) for restless legs syndrome as adjunctive and monotherapy: an individual participant data systematic review and meta-analysis. *Sleep Med*. 2026; 140: 108810. doi: 10.1016/j.sleep.2026.108810
31. Lin YC, Feng Y, Zhan SQ, et al. Repetitive Transcranial Magnetic Stimulation for the Treatment of Restless Legs Syndrome. *Chinese Medical Journal*. 2015; 128(13): 1728–1731. doi: 10.4103/0366-6999.159344
32. Heide AC, Winkler T, Helms HJ, et al. Effects of transcutaneous spinal direct current stimulation in idiopathic restless legs patients. *Brain Stimul*. 2014; 7(5): 636–642. doi: 10.1016/j.brs.2014.06.008
33. Hu S, He X, Zhang Y, Hu S, He F, Zhao F, Zhang Q, et al. Effectiveness and safety of massage in the treatment of restless legs syndrome: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)*. 2020; 99(48): e23239. doi: 10.1097/MD.00000000000023239

Information about the authors

Irina M. Madaeva – Dr. Sc. (Med.), Chief Researcher, Laboratory of Somnology and Neurophysiology, Scientific Center for Family Health and Human Reproduction problems; e-mail: nightchild@mail.ru, <https://orcid.org/0000-0003-3423-7260>

Alena A. Pytkina – research assistant, Laboratory of Somnology and Neurophysiology, Scientific Center for Family Health and Human Reproduction problems; e-mail: alena.orlova.200@mail.ru, <https://orcid.org/0009-0006-0269-5928>