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Restless Legs Syndrome: A Comprehensive Review of Current Treatment Methods and the Disease's Impact on Quality of Life

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ABSTRACT

Introduction and Purpose of Research: Restless Leg Syndrome (RLS) or Willis-Ekbom disease, is a common neurological disorder significantly impacting one's sleep and quality of life. It often coexists with various health issues, including diabetes and cardiovascular diseases. **Aim of study:** The primary purpose of this research is to explore diverse therapeutic options for RLS which are tailored to individual patient needs. In order to understand the complex pathophysiology of the discussed disease, recent advancements are taken into account. **Material and Methods of Research:** The review is grounded in findings from 36 recent studies sourced through a systematic search of open-access databases, including PubMed and Google Scholar, focusing on literature published between 2004 and 2024.

Results: Adequate and effective management of RLS include non-pharmacological interventions, such as physical activity, acupuncture, yoga and near-infrared light therapy, which can complement pharmacotherapy or prevail as the primary treatment form. Iron therapy emerges as vital for many patients. The correlation between iron metabolism and RLS symptoms requires further analysis and research. Pharmacological strategies involve

dopaminergic medications, low-potency opioids, and benzodiazepines, with a target on minimizing side effects and dependency.

Conclusion: RLS affects approximately 5-10% of the population, severely disrupting sleep and daily functioning. The condition constrains individualized management, integrating non-pharmacological forms of treatment with pharmacological therapies to improve patient outcomes and reduce dependence on medication.

Keywords: Restless leg syndrome, Willis-Ekbom disease, sensorimotor disorder, neurotransmitter dysfunction

Introduction

Restless Leg syndrome (RLS), clinically referred to as Willis- Ekbom disease, has gained greater diagnostic recognition in the past few years. It is stated that it is one of the most commonly diagnosed sleep-related sensorimotor disorders worldwide, with an estimated prevalence of 5-10% [1]. The etiology of this neurological condition may be due to genetic and environmental factors. RLS may present in individuals with comorbidities such as cardiovascular diseases, diabetes mellitus, hypertension or it may occur as a primary disease. [2] The aforementioned disease may affect both, the young and elderly populations, with a noted increase in symptom severity correlating with later time of disease onset.[3] The vast majority of RLS symptoms occur in the evening and are characterized by an unbearable urge to move the legs due to discomfort, accompanied by a burning or irritating sensation in the lower limbs, which is often relieved by activity or massage. Specific criteria have been made to help clinicians in accurate identification of the disease. These criteria encompass five vital components: 1. An irresistible urge to move legs, usually accompanied by uncomfortable sensations in lower extremities; 2. The onset or exacerbation of symptoms begin during periods of rest; 3. Physical activity leads to partial or complete alleviation of symptoms; 4. There is a nocturnal predominance of these symptoms, in comparison to their diurnal manifestation; 5. The presented symptoms are not indicative of any other medical condition.[3] Diverse treatment options have resulted from the aforementioned improvements in diagnostic criteria and a better comprehension of the pathophysiology of RLS, which highlight the malfunction of dopamine pathway, abnormalities in iron metabolism and hereditary variables. Initially, pharmacological

treatment was focused on dopaminergic agents, however after long term usage, it has been observed that it does not lead to symptom relief. Currently, alternative therapeutic options have emerged such as pregabalin, gabapentin, oxycodone/naloxone, iron supplementation and medicinal mushrooms. What is more, non-pharmacological treatment presents promising outcome. [1,2,4] The growing recognition of RLS represents a critical step forward in understanding this complex condition. Ongoing research continues to uncover the convoluted mechanisms underlying its pathophysiology, enabling the evolution of comprehensive and effective treatment strategies. In order to provide insights into holistic care, this review covers currently used therapy options for RLS.

Purpose of the study

The aim of this review is to analyze in depth various therapeutic approaches for patients suffering from RLS, taking into account both pharmacological and non-pharmacological treatment methods. Considering that the aforementioned disease affects one's quality of life in tremendous ways, it is crucial to understand its complex pathophysiology and tailor therapy to the individual patient's needs.

Review methods

This review is based on findings from 36 recent studies selected through a systematic search of open-access databases, including PubMed and Google Scholar. The selection process prioritized studies published between 2004 and 2024 to ensure a comprehensive and up-to-date analysis of restless leg syndrome management. Emphasis was placed on evidence-based data, covering a broad range of topics such as pathophysiology, diagnostic criteria, pharmacological therapies, and non-pharmacological treatment options. The inclusion of diverse methodologies and study designs augments the reliability and applicability of the review's conclusions.

Restless leg syndrome

Restless leg syndrome (RLS) is a complex, primarily idiopathic condition, which may have a hereditary component. It may present in association with other medical conditions including iron deficiency, uremia and polyneuropathy. [5] The clinical manifestation is mainly nocturnal, as the body shifts towards rest. Patients report a prickly or stinging sensation in their lower extremities, which may also affect the upper limbs. This discomfort is often intolerable by individuals and forces patients to move and massage their limbs in order to alleviate symptoms. [2]

The pathophysiology of RLS is defined as a triad of interrelated dysfunctions involving dopamine, iron and genetic factors. The dopamine pathway is of primary importance, since it has been noted that dopaminergic drugs are highly effective in treating RLS. Recent data suggests that the improperly functioning dopaminergic pathway lies within the small diencephalospinal tract which as a consequence influences the excitability of the spinal sensorimotor circuits. What is more, abnormalities within the endogenous opioid circuits and iron metabolism may intersect with the dopaminergic signaling. [6] It is vital for the clinicians to accurately distinguish RLS from other disorders presenting overlapping symptoms and identify the secondary forms, through evaluating the underlying conditions. [7] Diagnosis of RLS can be supported by a positive family history, occurrence of sleep disturbances, positive response to dopaminergic agents. Restless leg syndrome, may appear as an easily manageable disease, yet it is a challenge for the clinician to effectively and promptly alleviate one's symptoms. RLS significantly affects the quality of life of affected individuals, primarily due to compromised sleep. The current advancement in the understanding of the disease and underlying mechanisms has resulted in novel pharmacological and non-pharmacological treatment methods. [6,7]

Non-pharmacological treatment

Effective management of restless legs syndrome (RLS) is essential for affected individuals. Non-pharmacological interventions are a key component of treatment and can be administered in combination with pharmacotherapy or solely. These forms of therapy include activities such as everyday walking, taking warm/cool baths, extensive physical exercise and massages.[8] Despite the fact that these approaches are considered safe, there is no sufficient data to recognize their efficacy. Nonetheless, they may serve as to reduce the need for increased dosages of pharmacological treatments when recommended as adjunctive therapies. [9] Moreover, the non-pharmacological therapy may be suggested as a primary treatment option. However, in advanced stages of treatment, they may be only supportive to the pharmacological therapy. Patients are advised to improve their understanding of RLS, in order to develop preventative strategies. [10] Such proactive measures may include the avoidance of caffeine and alcohol which mare alleviate the symptoms. [11]

Acupuncture

Acupuncture is as beneficial form of therapy, particularly when combined with other therapies for RLS. It is a safe and effective treatment for neurological and psychiatric conditions. Research suggests that acupuncture may modulate the autonomic nervous system by inhibiting sympathetic nerve responses and mitigating excitatory cardiovascular reflexes via opioid pathways. The efficacy rates of acupuncture compared to non-acupuncture therapies show significant differences, with cure rates of 48% versus 22%. [12]

Near-infrared light therapy

Near-infrared (NIR) light therapy, is a part of the electromagnetic spectrum between visible light and radio waves. It is suggested as a safer and more efficient alternative compared to traditional acupuncture for stimulating acupoints. Recent findings suggest that NIR exposure may facilitate the release of nitric oxide from vascular endothelial cells, thereby enhancing peripheral circulation and facilitating sustained vasodilation. Nitric oxide, functioning as a neurotransmitter, plays a pivotal role in the process of neurotransmission. Additionally, NIR light therapy has presented promising effects on pain, a critical part of RLS. [13]

Yoga

Randomized controlled trials mention that yoga may provide a safe and effective alternative for alleviating RLS symptoms, reducing symptom severity, improving sleep and mood disturbances in adults experiencing RLS. However, larger randomized controlled trials are required to confirm these potential benefits. [14]

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive method for altering cortical excitability, has been proposed as a promising treatment approach for disorders characterized by brain hyperexcitability or hypoexcitability. TMS can safely deliver stimuli to brain neurons in the cerebral cortex. TMS has shown specific modifications in cortical excitability and plasticity, particularly concerning dysfunctional inhibitory mechanisms and sensorimotor integration which are believed to be the key component of RLS pathophysiology. High-frequency rTMS has shown significant efficacy in alleviating symptoms in the motor system, sleep disturbances and anxiety in RLS patients. These observations suggest that it may be an effective treatment option for this condition. [15,16]

Cryotherapy

While treatment for RLS primarily relies on pharmacological agents, many patients report symptom relief through cryotherapy. Data implies that whole-body cryotherapy at -60°C, as well as localized cryotherapy, may be implemented as a supplementary option for managing RLS with traditional pharmacological therapies. The precise mechanism of cryotherapy requires further research. [17]

Thermotherapy

Thermotherapy is commonly employed to treat musculoskeletal pain, with wet thermotherapy proving to be more effective than dry thermotherapy, due to the superior thermal conductivity of water compared to air. This treatment modality enhances skin temperature and promotes increased blood circulation, thereby improving the delivery of proteins, nutrients and oxygen, which may lead to symptom alleviation. Cryotherapy is known to elevate leukocyte levels while reducing histamine concentrations. What is more, evidence states that cryotherapy can boost plasma norepinephrine levels, thereby promoting neurotransmitter release.

On balance, both warm and cold-water treatments may ease RLS symptoms, with the findings suggesting cold water may be more effective for symptom reduction depending on individual preferences. [18]

In summary, the incorporation of non-pharmacological treatments not only improves patient outcomes but also has the potential to reduce dependence on higher doses of pharmacological agents, highlighting a promising direction for integrated management of RLS.

Pharmacological treatment

Pharmacological treatment is the core of Restless Legs Syndrome management, with personalized therapy methods based on the severity and persistence of symptoms. This section of the review provides a thorough approach to pharmacotherapy tailored for different RLS subtypes, emphasizing the use of targeted medications, iron therapy and adjunctive strategies. Moreover, it explores variations in specific treatments, including their indications, dosages, potential side effects and clinical preferences, providing a detailed guide to optimizing care for individuals suffering from RLS.

Table 1. RLS subtypes- approach to management. [19]

Restless leg syndrome treatment options		
Intermittent RLS	Symptoms occur less than 2x a week, are troublesome to the extent that treatment is necessary.	Non pharmacological therapy On demand medications: 1.Levodopa 2.Benzodiazepines 3. Low potency opioids (codeine, tramadol)
Chronic Persistent RLS	Symptoms require daily treatment, occur at least 2x a week and result in moderate or severe distress	Non pharmacological therapy Alpha-2-delta calcium channel ligands (gabapentin, pregabalin)
Refractory RLS	Unresponsive to monotherapy	Checkup of iron storage levels Opioid monotherapy Combination therapy (dopamine agonist, alpha-2-delta ligand, opioids, benzodiazepine)

Iron therapy

Iron therapy is an important treatment strategy for patients suffering from Restless Legs Syndrome. Recent studies in this field of medicine have proven the significance of iron supplementation in the pathophysiology of RLS, as well as the beneficial effects of iron supplementation on alleviating its symptoms.[19] However, the relationship between iron metabolism and the exacerbation of RLS remains uncertain. [20] Many individuals affected by this condition present blood tests with iron levels that are below the normal level, therefore, it is crucial to evaluate iron status even when there are no symptoms of deficiency.

This assessment should involve analysis of serum iron, ferritin, total iron-binding capacity and transferrin saturation percentage. Due to the fact that there are circadian rhythm alterations in serum iron levels- which are noted to be highest in the morning and lowest in the evening, the rise in serum iron levels post-meal and serum iron being considered as an independent indicator

of iron status, it is advised that these tests are performed in the morning after an overnight extended fast. Ideally, the final meal before fasting should include limited amount of meat. [21]

Serum ferritin, transferrin saturation, serum iron and total iron-binding capacity should all be included in a complete iron profile. Given its high cost and limited usefulness in non-anemic individuals, the soluble transferrin receptor is usually excluded from routine evaluations, despite the fact that it may offer additional information. Iron supplementation may be of benefit for RLS patients, but its effects on people with normal ferritin levels remain unknown.[22] Clinical research investigating oral and intravenous iron supplementation have substantially increased in recent years. Since intravenous iron is believed to promptly restore iron levels in comparison to oral administration, it is the recommended choice of therapy for patients who cannot tolerate oral iron or when oral therapy is not sufficient to compensate rapid iron loss, such as in cases of acute blood loss. [23,24]

Table. 2 Iron supplementation scheme. [19]

Iron supplementation scheme		
Diagnostic results	Administration route and dose	Drug dosage
Serum ferritin 75 mg/L Transferrin saturation <45%	Oral iron supplementation	325 mg of ferrous sulfate; 65 mg of elemental iron with 100-200mg of vitamin C, taken once daily or every second day.
Serum ferritin 75-100 mg/L Transferrin saturation <45%	Intravenous iron supplementation	Ferric carboxymaltose 1000 mg (as single or 2x500 mg) at 5-to-7-day intervals.
		Low-molecular-weight iron dextran 1000mg as a single infusion
		Ferumoxytol 1020mg as single infusion.

Treatment with carbidopa/levodopa

It is recommended to prescribe carbidopa or levodopa medication at a dose of 25 mg/100 mg in instances when the patient struggles to fall asleep due to the discomfort felt in their extremities or if the RLS symptoms keep them awake.[19] It is crucial to inform the patient, that the absorption can be compromised when taken with high-protein foods.

The following clinical criteria are considered to determine whether levodopa should be preferred over other medications: within few months, 80% of patients taking levodopa for RLS experience deteriorating symptoms; one-third of these patients experience depression, hypochondriac concerns or suicidal thoughts. The necessity of raising dosages is a significant issue that follows levodopa treatment. Patients report an early onset of symptoms during the day. What is more, duration and quality of sleep are decreased. Due to the fact that levodopa has the potential to cause increases in dosage, the pharmacological approach to levodopa, which was once believed to be the treatment of choice, has changed in recent years and has become effective only in patients presenting intermittent symptoms. [10, 25,26]

Low potency opioids (codeine/tramadol)

Due to the greater attention given by higher authorities and increasing concerns regarding the high rates of addiction and overdose in recent years, clinicians are becoming more reluctant to prescribe long-term opioids. Patients should be questioned about past and current psychiatric conditions, as well as any personal or family history of alcohol or drug misuse. Men and younger individuals are more likely to develop opioid dependence as a result of these features. The reasoning underlying an opioid prescription should be documented in medical records and the patient should be informed about possible alternative therapies. [27]

The aforementioned low potency opioids such as codeine (30-90 mg) or tramadol (50-100 mg) should be taken before bedtime or during the night in combination with acetaminophen. It should be stated that complete relief of symptoms is not attainable as a long-term goal in most patients. The possible side effects that a RLS patient may experience are sleepiness, nausea, constipation, pruritus, myoclonus and cognitive impairment. For patients with RLS who are not responding to other treatment, low-dose prescription opioids are becoming a common clinical treatment. [28]

Benzodiazepines

Benzodiazepines may be prescribed to patients who suffer from sleeplessness. Short-acting medications such as zolpidem (5–10 mg) or zaleplon (5–10 mg) could help individuals who struggle with insomnia and RLS. It is crucial to be aware of the benefits of intermediate-acting medications, such as temazepam (15–30 mg) and eczopiclone (1–3 mg), especially in circumstances where the patient gets awoken by RLS through the night. For women and the elderly, lower dosages of drugs are advised. [19]

The drugs of choice are pregabaline or gabapentin, which are administered once or twice a day either prior to sleep or later in the afternoon before RLS symptoms appear. The course of treatment takes place in a stepwise manner. Clinicians begin pharmacotherapy with 300 mg of gabapentin (100 mg for patients over 65) or 75 mg of pregabalin per day (50 mg for patients over 65). Within a few days, the dosage should be adjusted. In the majority of RLS cases a dose of 1200–1800 mg of gabapentin is necessary each day. The typical range for effective pregabalin dosages is 150–450 mg per day. Gabapentin should be used once or twice a day, late in the afternoon or evening or shortly before bed, unless RLS symptoms last for the majority of the day. [19,29]

Adverse effects of benzodiazepine therapy include day-time drowsiness, dizziness, unsteadiness and cognitive disturbances. All those reactions may be more frequent in older individuals. What is more edema, weight gain, depression and suicidal tendencies may also become apparent. [19,30]

Significance of the article

This review article is highly pertinent, as it addresses the critical need for accurate diagnosis and thorough management of Restless Legs Syndrome, a condition that has often been neglected due to its nonspecific symptoms and diagnostic challenges. By offering a detailed overview of the disease, its symptoms and a various treatment options, the article serves as an invaluable resource for both healthcare professionals and patients. It highlights the importance of prompt and accurate diagnosis and presents a range of therapies, from noninvasive methods, like yoga and infrared therapy to more potent pharmacological treatments, such as opioids, which require a caution and monitored use. The article presents current knowledge on RLS diagnosis and treatment, aiming to enhance clinical understanding and enable a more effective

management of the disorder, ultimately improving patient outcomes and supporting a more informed approach to care.

The Disease's Impact on Quality of Life

Following a thorough examination of research and results concerning Restless Legs Syndrome, a few significant points stand out:

Personalized treatment strategies: It is essential to keep in mind that Restless Legs Syndrome manifests variably in terms of both form and symptom intensity among individuals. It is crucial for therapeutic approaches to be tailored to each patient's specific needs. Treatment regimens and pharmacological combinations should be developed based on the particular symptoms experienced and their severity, rather than adhering to standardized protocols. For instance, some patients may benefit from a regimen that includes iron supplementation, rigorous physical activity and low-dose opioids. In contrast, others may find relief through simpler treatment plans, such as yoga or infrared therapy. A thorough understanding of this condition is vital for clinicians to effectively assess the complexities of this disorder.

The Impact of Restless Legs Syndrome on Quality of Life: Restless Legs Syndrome is a condition that in many cases is underestimated when it comes to its effects on one's health. RLS profoundly affects the quality of life for those who suffer from it, particularly individuals with additional health challenges, such as multiple sclerosis and Parkinson's disease. [31] Many patients with RLS have reduced functional abilities, increased levels of anxiety, depression and poor sleep quality. Based on recent studies, it has been proven that patients with RLS often report significant mental health difficulties, as evidenced by higher scores on the Hospital Anxiety and Depression Scale. While a clear connection between RLS and mental health issues is apparent in certain populations, this relationship is not consistent across all disorders. On balance, the burden of RLS can be compared with other chronic illnesses, leading to serious sleep disruptions and related mental health challenges. [32]

Influence of RLS on mental health: There is a notable connection between Restless Legs Syndrome and the prevalence of psychiatric disorders, depression in particular. Studies indicate that patients suffering from RLS are significantly more likely to experience depressive symptoms compared to individuals who do not struggle with the aforementioned condition. The odds ratio of having mild depression is nearly twice as high ($OR=1.95$, $p<0.001$). The odds

increase dramatically for moderate depression (OR=6.15, p<0.001), whereas for severe depression, the odds are (OR=56.54, p<0.001). The concerning data is that 97% of RLS patients suffering from depression report severe symptoms. Sleep disruptions are also common in this group, with severe depression linked to a variety of disturbances, such as difficulties falling asleep (OR=8.16, p<0.001), disrupted sleep (OR=11.66, p=0.001), waking early in the morning (OR=8.5, p<0.001), and daytime fatigue (OR=3.04, p=0.031). [33] The prevalence of depression among individuals with Restless Legs Syndrome ranges from 18% to 71%, while a study that investigated the prevalence of RLS among individuals with depression found a rate of 27%. [34], [35]

Consequences of neglecting RLS treatment: Ignoring the severity of RLS and its impact on one's life can lead to serious consequences, including an increased risk of self-harm and suicide. There is evidence of a connection between RLS and various chronic health conditions. A significant increase in mortality rates, estimated to be between 30% and 90%, has been observed. A study involving a population of 24,179 individuals, aged 20 to 65, with a documented history of RLS was conducted from 2009 to 2014. It has been noted that patients with RLS faced a noticeably higher risk of self-harm or suicide. Specifically, a ratio of 2.66 (95% confidence interval) was reported after adjusting for factors such as age, gender and other health issues. Throughout the five years of observation, there were 119 documented cases of suicide or self-harm in a larger study group of 169,373 individuals. These results highlight the concerning relationship between RLS and self-harming behaviors, emphasizing the urgent need for effective treatment to reduce these risks. [36]

Conclusion

In conclusion, Restless Leg Syndrome is a prevalent neurological disorder that has a significant impact on both sleep quality and overall quality of life for those affected. With a considerable number of population experiencing its symptoms, particularly during the evening hours, RLS requires notable attention, especially given its association with other health conditions such as diabetes and cardiovascular diseases. The recent understanding of the multimodal etiology of RLS, including dopamine dysfunction, iron metabolism anomalies and predisposing genetic factors, has facilitated the development of diverse treatment modalities. Both pharmacological and non-pharmacological approaches provide hope for the management and symptom relief. As research continues to evolve, inclusive management care strategies, comprise these variable

treatment options. Such actions will be crucial in improving the standard of life of individuals living with this challenging disorder.

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References

[1] Bugnicourt JM. Medicinal Mushroom, Ganoderma Lucidum, Improves Painful Symptoms in Patients with Restless Legs Syndrome. Clinical Studies & Medical Case Reports. 2023; 10(4): 1-4.https://doi.org/10.24966/csmc-8801/1000179

[2] Trenkwalder C, Allen R, Hogl B, et al.Comorbidities, Treatment, and Pathophysiology in Restless Legs Syndrome.The Lancet Neurology. 2018;17(10):994-1005. https://doi.org/10.1016/s1474-4422(18)30311-9

[3] Leclair-Visonneau L, Vecchierini MF, Schröder C, et al. How to diagnose restless legs syndrome. Revue Neurologique. 2018;174(7-8):508-514. https://doi.org/10.1016/j.neurol.2018.06.001

[4] Winkelmann J, Allen R., Högl B,et al.Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice. Movement Disorders. 2018;33(7):1077-1091. https://doi.org/10.1002/mds.27260.

[5] Khachatryan S, Ferri S. Fulda D, et al. Restless legs syndrome: Over 50 years of European contribution. Journal of Sleep Research. 2022;31(4). https://doi.org/10.1111/jsr.13632.

[6] Salminen A, Winkelmann J. Restless Legs Syndrome and Other Movement Disorders of Sleep—Treatment Update.Current Treatment Options in Neurology. 2018;20(12). https://doi.org/10.1007/s11940-018-0540-3.

[7] Brindani F, Vitetta F, Gemignani F. Restless legs syndrome: differential diagnosis and management with pramipexole. Clinal Interventions in Aging. 2009. https://doi.org/10.2147/cia.s4143

[8] Gossard TR, Trotti LM, Videnovic A, et al. Restless Legs Syndrome: Contemporary Diagnosis and Treatment. Neurotherapeutics. 2021;18(1):140-155 https://doi.org/10.1007/s13311-021-01019-4.

[9] Liu, Zhao MM, Guan, et al. Exploration of restless legs syndrome under the new concept: A review. Medicine. 2022;(101) 50 https://doi.org/10.1097/md.0000000000032324.

[10] Vlasie A, Trifu SC, Lupuleac C, et al. Restless legs syndrome: An overview of pathophysiology, comorbidities and therapeutic approaches (Review). Experimental and Therapeutic Medicine. 2021;23 (2). https://doi.org/10.3892/etm.2021.11108

[11] Ratnani G, Harjpal P. Advancements in Restless Leg Syndrome Management: A Review of Physiotherapeutic Modalities and Their Efficacy. Cureus. 2023. https://doi.org/10.7759/cureus.46779.

[12] Huang C, Tang J, Sun W, et al. Effectiveness of acupuncture in the management of restless leg syndrome: a systematic review and meta-analysis. Annals of palliative medicine. 2021;10 (10) https://doi.org/10.21037/apm-21-2309.

[13] Mohammadi M, Raygan AAV, Ghobadi A, et al. Effect of Near-Infrared Light Therapy Based on Acupoints on the Severity of Restless Legs Syndrome in Patients Undergoing Hemodialysis: A Single-Blind, Randomized Controlled Trial. Clinical Medicine & Research. 2018; 16 (1-2): 1-8.
https://doi.org/10.3121/cmr.2018.1389.

[14] Innes K, Selfe T, Montgomery CJ, et al. N. Effects of a 12-week yoga versus a 12-week educational film intervention on symptoms of restless legs syndrome and related outcomes: an exploratory randomized controlled trial. Journal of clinical sleep medicine. 2020; 16(1): 107-119. https://doi.org/10.5664/jcsm.8134.

[15] Nardone R, Sebastianelli L, Versace V, et al. Contribution of transcranial magnetic stimulation in restless legs syndrome: pathophysiological insights and therapeutical approaches. Sleep Medicine. 2020; 71. https://doi.org/10.1016/j.sleep.2019.12.009.

[16] 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. https://doi.org/10.4103/0366-6999.159344.

[17] Happe S, Evers S, Thiedemann C, et al. Whole body and local cryotherapy in restless legs syndrome: A randomized, single-blind, controlled parallel group pilot study. Journal of the Neurological Sciences. 2016;370. https://doi.org/10.1016/j.jns.2016.09.006.

[18] Jafarimanesh H, Vakilian K, Mobasseri S. Thermo-therapy and cryotherapy to decrease the symptoms of restless leg syndrome during the pregnancy: A randomized clinical trial. Complement Therapies in Medicine. 2020;50. https://doi.org/10.1016/j.ctim.2020.102409

[19] Silber MH, Buchfuhrer MJ, Earley CJ. , et al. The Management of Restless Legs Syndrome: An Updated Algorithm. Mayo Clinic Proceeding.2021; 96(7): 1921-1937.
https://doi.org/10.1016/j.mayocp

[20] 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 Medicine. 2018;42.
https://doi.org/10.1016/j.sleep.2017.11.1126

[21] Pengyu Zeng, Tiantian Wang, Lisan Zhang et al.Exploring the causes of augmentation in restless legs syndrome. Frontiers in Neurology. 2023;14. https://doi.org/10.3389/fneur.2023.1160112.

[22] Xuan Z, Juncong D, Yi-ren L, et al. The Efficacy and Safety of Pharmacological Treatments for Restless Legs Syndrome: Systemic Review and Network Meta-Analysis.Frontiers in Neuroscience. 2021;15. https://doi.org/10.3389/fnins.2021.751643.

[23] Kwatra V, Khan MA, Quadri SA, et al. Differential Diagnosis and Treatment of Restless Legs Syndrome: A Literature Review. Cureus. 2018. https://doi.org/10.7759/cureus.3297.

[24] Trotti L, Becker L. Iron for the treatment of restless legs syndrome. Cochrane database of systematic reviews. 2019. https://doi.org/10.1002/14651858.CD007834.pub3.

[25] Romero-Peralta S, Cano-Pumarega I, García-Borreguero D. Emerging Concepts of the Pathophysiology and Adverse Outcomes of Restless Legs Syndrome. Chest. 2020; 158(3): 1218-1229. https://doi.org/10.1016/j.chest.2020.03.035.

[26] Massey T, Robertson NP. Restless legs syndrome: causes and consequences. Journal of Neurology. 2020;267(2): 575-577. https://doi.org/10.1007/s00415-019-09682-6.

[27] Silber M, Becker P, Buchfuhrer M, et al. The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome. Mayo Clinic Proceedings.2018; 93(1):59-67. https://doi.org/10.1016/j.mayocp.2017.11.007.

[28] Winkelman JW, Purks J, Wipper B. Baseline and 1-year longitudinal data from the National Restless Legs Syndrome Opioid Registry. Sleep. 2021. https://doi.org/10.1093/sleep/zsaa183.

[29] Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. Mayo Clinic Proceedings. 2004;79(7): 916-922. https://doi.org/10.4065/79.7.916.

[30] Walters AS, Spruyt K, Ba DM, et al. A Historical Overview of the Role of Benzodiazepines including Clonazepam in the Treatment of Adult Restless Legs Syndrome and Periodic Limb Movements in Sleep. Tremor Other Hyperkinet Movements. 2024;14(1). https://doi.org/10.5334/tohm.824.

[31] An, Tianyang, et al. "Associations of Anxiety and Depression with Restless Leg Syndrome: A Systematic Review and Meta-Analysis." Frontiers in Neurology, vol. 15, 18 Mar. 2024, https://doi.org/10.3389/fneur.2024.1366839.

[32] Earley, Christopher J., and Michael H. Silber. "Restless Legs Syndrome: Understanding Its Consequences and the Need for Better Treatment." Sleep Medicine, vol. 11, no. 9, Oct. 2010, pp. 807–815, https://doi.org/10.1016/j.sleep.2010.07.007.

[33] Cho, Chul-Hyun, et al. "Individuals with Restless Legs Syndrome Tend to Have Severe Depressive Symptoms: Findings from a Community-Based Cohort Study." Psychiatry Investigation, vol. 14, no. 6, 2017, p. 887, https://doi.org/10.4306/pi.2017.14.6.887.

[34] Rin Miyaguchi, et al. “Prevalence of Depression or Depressive State in Patients with Restless Legs Syndrome: A Systematic Review and Meta-Analysis.” Sleep Medicine Reviews, vol. 77, 11 July 2024, pp. 101975–101975, https://doi.org/10.1016/j.smrv.2024.101975.

[35] Gupta, Ravi, et al. “Prevalence of Restless Leg Syndrome in Subjects with Depressive Disorder.” Indian Journal of Psychiatry, vol. 55, no. 1, 2013, p. 70, https://doi.org/10.4103/0019-5545.105515.

[36] Massey, T. H., and N. P. Robertson. “Restless Legs Syndrome: Causes and Consequences.” Journal of Neurology, vol. 267, no. 2, 7 Jan. 2020, pp. 575–577, https://doi.org/10.1007/s00415-019-09682-6.