Therapy of Childhood Restless Legs Syndrome and Periodic Limb Movement Disorder

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KEYWORDS

• Restless legs syndrome • Periodic limb movement disorder • Treatment • Iron supplementation • Dopaminergics • Non-pharmacologic treatment

KEY POINTS

- Effective management of pediatric Restless Legs Syndrome/Periodic Limb Movement Disorder (RLS/PLMD) requires a blend of pharmacologic and non-pharmacologic interventions tailored to each child's needs, including traditional and emerging therapies.
- Studies suggest iron supplementation can improve sleep and alleviate symptoms in children with RLS and PLMD, with both oral and intravenous options showing promise.
- While dopaminergic therapies and antiepileptic agents have shown potential benefits, evidence in pediatric populations remains limited compared to adults.
- Lifestyle changes like better sleep, diet, exercise, and avoiding certain medications help manage pediatric RLS and PLMD, often before medication is considered.
- Regular follow-up assessments are crucial to monitor treatment efficacy and adjust strategies as needed, ensuring optimal management and improving outcomes for children with RLS and PLMD.

INTRODUCTION

Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)[1] are prevalent sleep disorders affecting pediatric populations, often posing significant challenges to both affected individuals and healthcare providers. Characterized by uncomfortable sensations in the legs and an irresistible urge to move them,[2] RLS disrupts sleep onset and maintenance, leading to daytime fatigue and impaired quality-of-life. Similarly, PLMD manifests as repetitive limb movements during sleep, known as periodic leg movements during sleep (PLMS), further exacerbating sleep disturbances and contributing to neurocognitive deficits. PLMS are associated with increased sympathetic activation, leading to increased heart rate[3] and blood pressure changes,[4] which can lead to sleep

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Abbreviations	
ADHD	attention-deficit/hyperactivity disorder
ASD	Autism Spectrum Disorder
FDA	Food and Drug Administration
IV	intravenous
PLMD	Periodic Limb Movement Disorder
PLMS	periodic leg movements during sleep
RLS	Restless Legs Syndrome
RSD	Restless Sleep Disorder

fragmentation. The movement itself can also be a sleep disrupter either triggering arousals[5] or sleep stage shifts. Childhood is an important period during which neuronal connections are built and pruned, especially during sleep[6]; therefore, sleep fragmentation, altered sleep architecture, and insufficient sleep can compromise these neurocognitive networks.

The management of pediatric RLS and PLMD demands a multifaceted approach, integrating both pharmacologic and non-pharmacologic interventions tailored to the unique needs of children and adolescents. While traditional treatments targeting iron deficiency and dopamine dysfunction remain fundamental, novel therapeutic modalities continue to emerge, offering promising avenues for symptom alleviation, and improved sleep quality.[7,8]

This article aims to provide a comprehensive overview of the current landscape of treatment options for pediatric RLS and PLMD. Through an exploration of evidence-based strategies, including lifestyle modifications, pharmacotherapy, and emerging interventions, we aim to provide healthcare providers the knowledge and tools necessary to effectively manage these sleep disorders in pediatric patients. Additionally, we will approach also the complexity of treatment selection, dosing considerations, and long-term management strategies, with a focus on optimizing outcomes and enhancing the well-being of children affected by RLS and PLMD.

By attempting to unfold the complexities of pediatric RLS and PLMD management, this article seeks to empower clinicians with the insights and resources needed to navigate the challenges inherent in treating these sleep disorders, ultimately fostering improved sleep health and quality-of-life for pediatric patients and their families.

IRON AND PEDIATRIC SLEEP

Several studies have investigated the effects of iron supplementation on pediatric sleep, providing valuable insights into the potential benefits of addressing iron deficiency in the management of RLS and PLMD. Dosman and colleagues[9] conducted a study focusing on children with autism, a population known to be at increased risk of sleep disturbances. Their findings demonstrated a significant improvement in sleep reported in the Sleep Disturbance Scale for Children[10] following iron supplementation, highlighting the potential role of iron in addressing sleep issues in this population,; however, objective polysomnographic data were not included.

Similarly, Kordas and colleagues[11] investigated the effects of iron and/or zinc supplementation on sleep in infants from Nepal and Zanzibar. The results indicated that maternal reports of sleep improved with iron supplementation, suggesting a positive impact on sleep quality in young children.

Cortese and colleagues[12] examined the association between sleep disturbances and serum ferritin levels in children with attention-deficit/hyperactivity disorder (ADHD). Their study revealed a correlation between low serum ferritin levels and sleep disturbances, underscoring the potential relevance of iron status in pediatric sleep disorders.

Furthermore, Reynolds and colleagues[13] conducted a randomized, placebo-controlled trial to evaluate the efficacy of ferrous sulfate in treating insomnia in children with autism spectrum disorders (ASD). The results of this study showed promising outcomes, with iron supplementation leading to improvements in insomnia symptoms compared to placebo.

Iron and Ferritin in Pediatric Restless Legs Syndrome/Periodic Limb Movement Disorder

In addition to the evidence from studies focusing on specific pediatric populations, recent research has highlighted the association between low serum ferritin levels and PLMD in children. Liu and colleagues[14] reported serum ferritin levels of less than 50 ng/mL in children with PLMD, a finding consistent with those observed in children with RLS and Restless Sleep Disorder (RSD). Similarly, DelRosso and colleagues[15] found comparable serum ferritin levels in children with PLMD and those with PLMS index more than 5, further supporting the notion of iron deficiency as a potential contributing factor to PLMD.

The convergence of evidence from these studies underscores the rationale for considering iron supplementation as a therapeutic approach in pediatric RLS and PLMD. Given the association between low serum ferritin levels and sleep disturbances observed in various pediatric populations, addressing iron deficiency may offer a promising avenue for improving sleep quality and alleviating symptoms associated with RLS and PLMD.

It should be taken also into account that studies in adults have suggested that in patients with RLS, the level of ferritin in the cerebrospinal fluid is significantly lower than controls for the same level of ferritin in the serum.[16] Therefore, patients with RLS should not be treated with normative data for patients without RLS. The consensus in children is to supplement when ferritin levels are below 50 ng/mL, but more research is needed.

Iron Supplementation in Restless Legs Syndrome/Periodic Limb Movement Disorder

One study by Dye and colleagues[17] conducted a retrospective chart review of children with RLS or PLMD who were on iron supplementation for over 2 years. The study, which included 105 patients with an average age of 10.2 years, concluded that iron therapy appears to lead to long-lasting improvements in children with RLS/PLMD.

Another retrospective chart review, conducted by Gurbani and colleagues,[18] focused on children with RLS/PLMD and parasomnias. Among the 226 participants, 50 had parasomnias, and 30 of them were treated with elemental iron. The study found that RLS symptoms improved in 50% of the children, and parasomnias resolved in 40% after iron therapy. Post-treatment polysomnography showed a significant decrease in PLMS index and PLMS-related arousals.

DelRosso and colleagues[19] examined responders versus nonresponders to iron therapy (1 – 3 mg/kg/day elemental iron for 2 – 6 months) and concluded that side effects hinder adherence to oral iron supplementation in children.

In another study by Grim and colleagues,[20] the efficacy of oral iron supplementation and intravenous (IV) iron sucrose in children with RLS was investigated. The study found that while some subjects did not experience improvement with oral supplementation, IV iron sucrose resulted in improved sleep in a majority of subjects, with minor adverse events reported.

DelRosso and colleagues (2021)[21] assessed the impact of intravenous ferric carboxymaltose on iron parameters and clinical symptoms in children with RLS or PLMD. The study concluded that IV ferric carboxymaltose significantly improved serum ferritin levels and clinical symptoms, suggesting its efficacy as a treatment option.

Furthermore, DelRosso and colleagues[22] examined RLS symptoms in children with ASD and found a significant percentage of children with ASD exhibited RLS symptoms, indicating a need for further investigation and tailored management approaches.

Another study by Ingram and colleagues[23] involved 63 pediatric patients who underwent IV iron infusion, mostly with ferric carboxymaltose (n = 60), for RLS (n = 30), PLMD (n = 22), and RSD (n = 17). No significant differences were found between groups in terms of ferritin increase. Immediate adverse reactions to the IV infusion were observed in 7 (11%) children who experienced at least 1 side effect, with the most common being behavior change (n = 6) or gastrointestinal discomfort (n = 4); no episodes of anaphylaxis or extravasation were noted.

Lastly, DelRosso and colleagues[24] investigated the association between iron deficiency and periodic limb movements in infants. The study found that iron deficiency was associated with increased periodic limb movements, particularly in premature infants.

In summary, the rationale for using iron supplementation in pediatric RLS and PLMD is supported by a growing body of evidence demonstrating the potential benefits of correcting iron deficiency in improving sleep parameters and alleviating symptoms. Further research is warranted to elucidate the underlying mechanisms linking iron status to sleep disturbances in children and to optimize therapeutic strategies for managing these sleep disorders effectively.

However, a discrepancy can be noticed between the current guidelines, as established by Allen and colleagues,[25] and the recommendations made by specialists, such as those proposed by Earley in 2003,[26] regarding the use of oral iron supplementation for pediatric RLS/PLMD with serum ferritin levels below 50 ng/mL, which raises important considerations and highlights the complexity of managing these conditions. One possible explanation for this disparity could stem from the limitations of existing evidence. While studies have provided valuable insights into the potential benefits of iron supplementation for pediatric RLS and PLMD, including improvements in sleep parameters and symptom management, the evidence may not yet meet the rigorous standards required for guideline recommendations. Clinical guidelines typically rely on high-quality evidence from well-designed randomized controlled trials or meta-analyses to formulate recommendations. However, the available evidence may still be limited in quantity or quality, leading to cautious or conservative recommendations from guideline committees.

Furthermore, the discrepancy may also reflect the evolving nature of scientific understanding and clinical practice. As research continues to uncover the mechanisms underlying RLS and PLMD in children, including the potential role of

iron deficiency, clinical practice may outpace guideline recommendations. Specialists who regularly encounter pediatric patients with RLS and PLMD may incorporate emerging evidence and clinical experience into their practice, leading them to advocate for interventions like oral iron supplementation based on their observations of positive outcomes in individual patients.

Another factor contributing to the variation in recommendations could be the heterogeneity of pediatric RLS and PLMD. These conditions can manifest differently among children, with variations in symptom severity, underlying causes, and response to treatment.[27]

Pienczk-Ręclawowicz and colleagues[28] conducted a study revealing a significant association between RLS and low ferritin levels among pediatric patients. Their findings indicate that a striking 85% of children diagnosed with RLS exhibit serum ferritin levels below the clinically relevant threshold of 50 ng/mL. This high prevalence of iron deficiency among pediatric RLS patients underscores the potential importance of iron status in the development and manifestation of RLS symptoms. Given the established role of iron in dopamine metabolism and its involvement in the regulation of sleep-wake cycles, the observed association between iron deficiency and RLS in children aligns with the existing literature on the role of iron dysregulation in adult RLS.

However, the relationship between iron status and RLS may not be universal across all pediatric populations. Riar and colleagues[29] investigated iron and inflammation levels in children with RLS, specifically within the context of chronic kidney disease. Surprisingly, their findings indicated that neither ferritin nor inflammation levels differed significantly between children with RLS and those without RLS within the chronic kidney disease population. This suggests the presence of alternative pathophysiologic pathways contributing to RLS in this particular subgroup, distinct from the iron-related mechanisms observed in other pediatric RLS patients.

The disparity in iron status findings between different pediatric RLS populations highlights the heterogeneous nature of RLS and PLMD, with various underlying mechanisms potentially contributing to their manifestation. As a result, a personalized approach to management may be warranted with clinicians considering factors, such as serum ferritin levels, symptom severity, comorbidities, and individual patient characteristics when making treatment decisions.

In light of these considerations, it is important for clinicians to critically evaluate the available evidence, consider expert opinions, and engage in shared decision-making with patients and their families when determining the most appropriate management approach for pediatric RLS and PLMD. While guideline recommendations[25] provide valuable guidance, they should be viewed as a starting point rather than a rigid framework, with clinical judgment and individual patient considerations ultimately guiding treatment decisions. As research continues to advance and our understanding of these conditions deepens, future updates to guidelines may incorporate emerging evidence and further clarify the role of iron supplementation in the management of pediatric RLS and PLMD.

In addition, the absence of Food and Drug Administration (FDA)-approved medications specifically designated for treating RLS in children poses significant challenges for clinicians managing pediatric patients with this condition. Consequently, healthcare providers often resort to using medications that are approved for adults' off-label, tailoring dosages based on clinical experience and available evidence.[8]

In the realm of pharmacotherapy for pediatric RLS, oral iron preparations are commonly utilized, with dosages typically falling within the range of 3 to 6 mg/kg/day, as suggested by Mohri and colleagues[30] This dosage range aims to balance therapeutic efficacy with the risk of adverse effects, taking into account factors such as age, weight, and individual patient response. However, achieving symptom relief with these medications often requires patience, as it may take 3 months or longer before noticeable improvements are observed.[19] This protracted timeline underscores the importance of ongoing monitoring and patient education to manage expectations and optimize treatment outcomes.

Despite its potential benefits, iron supplementation for pediatric RLS is not without drawbacks. One of the most commonly reported side effects associated with this treatment is constipation,[19] which can significantly impact patient comfort and quality-of-life. Additionally, certain formulations, particularly liquid preparations, may carry an increased risk of teeth staining, posing cosmetic concerns for pediatric patients and their caregivers.

Although flavored oral iron preparations, such as iron polysaccharide complex, have been proposed with the promise of being better tolerated, the supplementation of ferrous sulfate once a day has been proven to be more effective and is the current recommendation for children.[31]

Picchietti[32] highlighted the importance of weighing the potential risks and benefits of pharmacotherapy in pediatric RLS, emphasizing the need

for close monitoring and proactive management of adverse effects to ensure optimal treatment outcomes.

DOPAMINERGIC THERAPIES

Among dopaminergic medications, there exists a categorization into levodopa and non-ergot derived dopamine agonists such as pramipexole, ropinirole, and rotigotine. Dopamine receptor agonists have gained approval for managing RLS in adults, their usage is widespread and supported by extensive efficacy data; although recent guidelines have introduced cautions in their use because of the frequent development of augmentation.[33] However, evidence supporting their application in pediatric RLS remains limited. Although dopaminergic medications have demonstrated success in individual case reports and small-scale open-label studies involving children with RLS, both with and without ADHD, few double-blind, placebo-controlled trials have been conducted.[8,34–39]

A noteworthy investigation in 2011[40] explored the impact of L-dopa on symptoms of both ADHD and RLS in children through a small randomized, double-blind study. This study, involving 29 children diagnosed with both ADHD and RLS, alongside 29 with ADHD alone, administered either L-dopa or a placebo. While significant improvements were observed in RLS and PLMS symptoms, there were no discernible effects on objective neuropsychiatric measures of ADHD. Despite the substantial clinical overlap between ADHD and RLS,[41,42] managing symptoms in this particular patient population often necessitates multiple therapeutic approaches, a subject beyond the scope of this discussion.

Furthermore, a case series conducted by Walters and colleagues[34] demonstrated promising results where monotherapy with either carbidopa/levodopa in 5 children or pergolide in 2 children led to improvements in RLS, PLMS, and daytime symptoms of ADHD. Additionally, individual case reports have highlighted significant improvements in both daytime and nighttime symptoms using dopaminergic agents such as ropinirole in a 6-year-old boy with ADHD and RLS,[35] and rotigotine in an 11-year-old girl with RLS and comorbid depression.[43]

The utilization of dopaminergics, sometimes in combination with iron supplementation, has also shown effectiveness in adolescents.[17,44] However, despite the potential benefits, there are notable limitations to their usage in adults, including augmentation, withdrawal symptoms, and various side effects such as nausea, sleepiness, insomnia, obsessive-compulsive behaviors, hallucinations, and augmentation. It is important to note that data regarding side effects in children remain limited, and there is a lack of information on augmentation specifically in pediatric populations. Thus, careful consideration and monitoring are essential when employing dopaminergic therapies, particularly in pediatric patients.

ANTIEPILEPTIC AGENTS

The utilization of antiepileptic medications for the treatment of RLS in pediatric patients has been the subject of limited investigation. While rare studies have explored the efficacy of carbamazepine[45] and valproic acid,[46] there remains insufficient evidence regarding their effectiveness in children. Consequently, this section will focus on discussing the available evidence pertaining to the usage of alpha-2-delta ligands and levetiracetam in pediatric RLS.

Alpha-2-Delta Ligands

Gabapentin, an alpha-2-delta-1 ligand commonly employed in the management of epilepsy and neuropathic pain, has emerged as a potential treatment option for pediatric RLS. Its long-term use in children for these indications has demonstrated safety with minimal adverse effects, rendering it an appealing therapeutic choice for RLS. Predominantly, reported adverse reactions include sleepiness and dizziness. Polysomnography studies conducted in adults receiving gabapentin have indicated its impact on sleep architecture, notably enhancing slow-wave sleep while reducing sleep-onset latency.[47]

While gabapentin enacarbil holds FDA approval for addressing moderate to severe symptoms of RLS in adults, its use in children lacks formal endorsement. Nonetheless, isolated cases document its successful application in pediatric RLS. For instance, Amos and colleagues investigated various treatments, including iron, in children with RLS, wherein 2 children treated solely with gabapentin exhibited symptom resolution.[48]

Additionally, a case report detailed the effective use of gabapentin in a 14-month-old girl experiencing psychomotor retardation and severe chronic insomnia accompanied by distressing nocturnal leg movements suggestive of RLS. Following gabapentin administration at bedtime, immediate improvement in leg movements and sleep continuity was observed, with symptom disappearance upon dosage escalation.[49]

Levetiracetam

Levetiracetam, an antiepileptic agent with multifaceted mechanisms of action inhibiting neuronal

hyper-synchronization, has also garnered attention for its potential in managing pediatric RLS. Its activation of gamma-aminobutyric acid pathways may contribute to reported side effects such as somnolence and fatigue.[50] Notably, mood changes, depression, anxiety, and occasionally psychosis are among the most commonly reported adverse effects.[51]

One study involving 7 boys aged 5 to 12 years diagnosed with ADHD and RLS demonstrated promising outcomes with levetiracetam administration.[52] Starting at 10 to 20 mg/kg/day and incrementally increasing to 50 to 60 mg/kg/day over a period, improvements in symptoms and daytime behaviors were noted. Follow-up assessments at 3 and 6 months revealed enhancements in the International RLS Rating Scale scores and parental reports of improved sleep quality with fewer nocturnal awakenings. Notably, no adverse effects were reported during the course of treatment.[52]

BENZODIAZEPINES

Clonazepam

Clonazepam, a benzodiazepine with a long duration of action, is occasionally utilized to address frequent and disruptive parasomnias in pediatric patients. Its prolonged half-life may be advantageous for children who naturally experience extended sleep durations. While there exist limited data regarding their application in pediatric RLS, polysomnography studies have indicated its potential to enhance overall sleep quality and reduce arousal frequency in RLS patients. However, it appears less effective in mitigating the motor and sensory abnormalities associated with RLS.[53,54]

A study involving 51 children treated for PLMD, though not RLS, demonstrated that clonazepam was chosen as a first-line treatment in 6 cases, while a combination of dopamine agonist and clonazepam was employed in 5 cases.[55] The most commonly reported side effect of clonazepam was paradoxic alertness, occurring in approximately 13% of cases. However, despite its clinical usage, there remains a dearth of polysomnographic evidence substantiating its effectiveness.

OTHER TREATMENT OPTIONS

Clonidine

Clonidine, an alpha-2 adrenergic agonist, is frequently prescribed for insomnia, particularly in children with neurodevelopmental disorders, especially when accompanied by hyperactivity. Its soporific effects are attributed to its antiadrenergic properties, which mitigate overactivity of the sympathetic nervous system. Widely utilized as a pediatric sleep aid, clonidine is esteemed for its tolerability, rapid onset of action, and efficacy. There is also evidence suggesting its efficacy for RLS sensory symptoms in adults without significant side effects.[56]

Opioids

Opioids are typically reserved for cases of refractory RLS in adults due to their action on dopaminergic receptors. However, there is a notable absence of data regarding their use in pediatric populations.

Magnesium

Early studies have suggested a potential positive effect of magnesium on RLS and PLMD in adults and pregnant women.[57,58] Nevertheless, data regarding their efficacy and safety in children remain scarce.

Vitamin D

Recent research has proposed a correlation between vitamin D deficiency and the severity of RLS symptoms, with low vitamin D levels potentially contributing to dopaminergic dysfunction.[59] Although studies in adults have shown improvement in RLS symptoms with vitamin D supplementation, research in children is lacking.[60]

Melatonin

The worsening of RLS symptoms at night indicates a circadian preference, with peak symptom manifestation coinciding with peak melatonin production in the evening. Interactions between melatonin and dopamine pathways have been noted[61,62] with exogenous melatonin demonstrating effects on PLMS.[63] Despite its prescription for children with delayed circadian disorders or insomnia, evidence supporting its use in pediatric RLS or PLMD is currently insufficient.

NON-PHARMACOLOGIC APPROACHES TO MANAGING RESTLESS LEGS SYNDROME IN CHILDREN

In the comprehensive treatment of RLS in children, non-pharmacologic interventions play a pivotal role. Given that RLS often intertwines with difficulties in sleep onset, it is imperative to incorporate a review of sleep hygiene and bedtime routines into the treatment regimen. Establishing healthy sleep habits constitutes a fundamental aspect of a holistic treatment plan, encompassing factors such as ensuring adequate sleep duration, adhering to regular bedtimes, and upholding principles of good sleep hygiene. Consequently,

Table 1
Summary of the various treatment options for pediatric restless legs syndrome and periodic limb movement disorder, including both pharmacologic and non-pharmacologic interventions

Treatment Option	Description
Iron Supplementation	Oral or IV iron therapy to address iron deficiency, potentially improving sleep parameters and alleviating symptoms of RLS and PLMD.
Dopaminergic Therapies	Medications, such as levodopa, pramipexole, ropinirole, and rotigotine, that target dopamine receptors, though evidence in pediatric populations is limited.
Antiepileptic Agents	Use of medications like gabapentin and levetiracetam, with limited evidence but potential efficacy in managing RLS symptoms in children.
Benzodiazepines	Clonazepam may be used to address frequent and disruptive parasomnias associated with RLS and PLMD, though its effectiveness in children is not well studied.
Clonidine	Alpha-2 adrenergic agonist prescribed for insomnia, potentially helpful in managing RLS sensory symptoms in children, with few reported side effects.
Opioids	Reserved for refractory cases in adults, with limited data on their usage in pediatric populations due to their action on dopaminergic receptors.
Magnesium	Early studies suggest a potential positive effect on RLS and PLMD, but data in children remain scarce.
Vitamin D	Correlation between vitamin D deficiency and RLS severity has been proposed, with studies showing improvement in adults, but research in children is lacking.
Melatonin	May aid in symptom attenuation due to its interactions with dopamine pathways, though evidence supporting its use in pediatric RLS and PLMD is insufficient.
Non-Pharmacologic Interventions	Lifestyle modifications including sleep hygiene, dietary adjustments, physical activity, sensory stimulation, and avoidance of certain medications play a pivotal role in managing pediatric RLS and PLMD, often recommended before considering medication.

numerous activities can help alleviate RLS symptoms. Notably, as per RLS criteria, leg movements should alleviate symptoms, thereby suggesting that activities such as walking or stretching late in the afternoon and a few hours before bedtime may prove beneficial. This section will delve into the most common non-pharmacologic recommendations for pediatric RLS management.

Sleep Hygiene

Insomnia often emerges as the primary symptom in children with RLS.[64] Therefore, a thorough assessment of sleep habits, routines, and available opportunities for sleep is crucial in evaluating children with RLS and associated sleep onset difficulties. Sleep hygiene, in essence, revolves around providing ample opportunity for sleep and maintaining a consistent sleep schedule. The bedroom environment should foster optimal sleep conditions, characterized by a cool, dark, clean, and uncluttered space, equipped with a comfortable mattress and bedding. Additionally, it is imperative to advise children to disconnect from electronic devices at least an hour before bedtime. Although the singular effectiveness of sleep hygiene in managing RLS remains unassessed, implementing these recommendations can aid in identifying other potential confounders and contribute to overall improvements in sleep patterns.

Physical Activity

While stretching exercises prior to bedtime may offer relief conducive to falling asleep, engaging in strenuous exercise within a few hours of bedtime should be avoided. Studies in adults have demonstrated that aerobic exercise and lower body resistance training 3 times a week improved RLS symptoms,[65] possibly through mechanisms involving improved circulation or release of endorphins.[66] Specific stretching exercises, such as leg raises, have shown a significant decrease in RLS symptoms.[67]

Dietary Modifications

Reports have suggested that a gluten-free diet led to symptom improvement in RLS patients with celiac

Box 1
Algorithm for treatment of pediatric restless legs syndrome/periodic limb movement disorder

Step 1: Initial Assessment and Identification of Exacerbating Factors

1. *Patient History and Symptom Review:* Gather a comprehensive patient history and assess symptoms suggestive of RLS/PLMD.
2. *Identify Exacerbating Factors:*
   a. *Medication Review:* Check if the child is taking medications that could exacerbate RLS/PLMD, such as caffeine, antihistaminergic, serotonergic, and anti-dopaminergic medications. Consider adjusting or replacing these medications as appropriate.
   b. *Check for Obstructive Sleep Apnea (OSA):* Ask about snoring, observed apneas, or excessive daytime sleepiness. If OSA is suspected, proceed with a polysomnography for confirmation.

Step 2: Laboratory Tests

1. *Serum Ferritin and Iron Studies:*
   a. *Ferritin Testing:* Order fasting serum ferritin, iron, and total iron binding capacity (TIBC) with transferrin saturation percentage.
   b. *Testing Guidelines:* Ensure the child avoids all iron-containing supplements and foods for at least 24 hours before the blood draw.
   c. *Systemic Inflammation: order serum soluble transferrin when there is history of recent systemic inflammation.*

Step 3: Interpret Test Results and Determine Treatment Plan

1. *Ferritin <50 ng/mL:*
   a. *Oral Iron Supplementation:*
      i. Assess Tolerance: Determine if the child has previously tolerated oral iron supplements.
      ii. If Tolerated: Initiate oral iron supplementation *(2–5 mg/kg/day, on an empty stomach with orange juice)*.
      iii. Monitor for adverse effects such as gastrointestinal discomfort *or constipation*. Consider starting with low doses and gradually increasing to minimize side effects.
   b. *If Not Tolerated:* Consider intravenous (IV) iron treatment.
2. *Ferritin ≥50 ng/mL:*
   a. *Further Evaluation and Alternative Treatments:* If ferritin levels are adequate, consider other causes and discuss treatment options with a pediatric sleep specialist or neurologist. Potential interventions may include lifestyle changes, behavioral therapy, or pharmacologic treatments targeting underlying RLS/PLMD mechanisms.

Step 4: Follow-Up and Monitoring

1. *Regular Monitoring:*
   a. *Follow-Up on Iron Levels:* Recheck serum ferritin and iron studies after a few months of treatment to assess response and adjust supplementation as needed.
   b. *Monitor RLS/PLMD Symptoms:* Track symptom changes with regular follow-up visits to adjust treatment as necessary.
2. *Refer to Specialists:* If symptoms persist or worsen, or if underlying conditions require specialized care, refer to a pediatric neurologist, sleep specialist, or other appropriate healthcare professionals.

This algorithm should be used as a guideline and tailored to each individual child's clinical circumstances and needs. Always consult with relevant specialists to ensure the best care for pediatric patients with RLS/PLMD.

disease.[68] However, analogous reports in children are lacking. Furthermore, caffeine consumption has been linked to exacerbation of RLS symptoms, thus warranting avoidance of coffee, chocolate, or any other caffeinated substances in the afternoon.[48]

Sensory Stimulation

Although not extensively studied in RLS patients, some individuals report relief from RLS symptoms through activities such as rubbing, massaging, or

applying cool or heating pads.[69] Massage therapy, albeit not directly investigated in RLS patients, has been shown to increase dopamine levels, which may contribute to symptom improvement. Similarly, while vibration therapy has been studied in adults,[70] data regarding their efficacy in children with RLS is lacking.

Avoidance of Medications

Certain medications are known to exacerbate RLS symptoms, including selective serotonin reuptake inhibitors,[71] tricyclic antidepressants, metoclopramide, diphenhydramine, nicotine, and alcohol.[72] However, antidepressants with dopaminergic activity, such as bupropion and trazodone,[73,74] have not been associated with exacerbation of RLS symptoms. Thus, careful consideration of medication usage is imperative in managing RLS in children.

Support Groups

Support groups are vital in helping families manage RLS in children. The RLS Foundation in the United States (https://www.rls.org/) and the European Alliance for Restless Legs Syndrome (https://earls.eu/), along with several National organizations, are notable resources, providing information, advocacy, and a supportive community. They both offer educational content, guidance on coping strategies, and opportunities to connect with others facing similar challenges. Families can benefit from engaging with these groups to learn more about RLS, share experiences, and find emotional support. Online forums and social media groups are also great places to exchange advice and build a network of support. These connections can help parents navigate the complexities of RLS in children, fostering a sense of community and providing reassurance that they are not alone in their journey.

Finally, **Table 1** provides an overview of available treatment options, highlighting the diversity of approaches that can be considered in managing pediatric RLS and PLMD.

SUMMARY AND FUTURE PERSPECTIVES

In summary, the management of pediatric RLS and PLMD necessitates a comprehensive approach, with initial emphasis placed on non-pharmacologic interventions. Lifestyle modifications, including dietary adjustments, exercise regimens, and the avoidance of medications exacerbating the sensory-motor symptoms of RLS and PLMD, are pivotal strategies to mitigate symptoms and enhance overall well-being.

Evaluation of iron storage status is paramount in children presenting with RLS and PLMD, with iron supplementation remaining the cornerstone of treatment. In cases where oral iron supplementation fails to yield adequate improvement, IV iron therapy may be considered as an alternative option. However, in instances where iron deficiency is not a contributing factor or where significant comorbidities are present, exploration of alternative treatment modalities becomes necessary.

A comprehensive review of the evidence highlights various treatment options studied in the literature, encompassing the use of dopaminergics, benzodiazepines, anticonvulsants, and other less conventional therapies. Given the limited availability of robust data, a cautious approach is warranted, commencing with the lowest effective dosage and titrating slowly while closely monitoring for therapeutic efficacy and potential adverse effects.

Based on these considerations, a reference algorithm can be suggested for the treatment of pediatric RLS/PLMD, as shown in **Box 1**.

Furthermore, the natural progression of pediatric RLS and PLMD remains incompletely understood; however, preliminary evidence suggests a potential for symptom improvement over time. As such, treatment duration of approximately 6 months seems to be reasonable, followed by a period of observation to ascertain the evolution of symptoms. Regardless of the chosen therapeutic pathway or the decision for observation, regular follow-up assessments are essential to monitor the presence and severity of RLS and PLMD symptoms and adjust treatment strategies accordingly. By adopting a comprehensive and tailored approach, healthcare providers can optimize outcomes and improve the quality-of-life for children affected by RLS and PLMD.

CLINICS CARE POINTS

- Conduct a thorough assessment including sleep history, symptom severity, and potential underlying conditions to tailor treatment to the individual child's needs.
- Collaborate with specialists such as pediatric neurologists, sleep medicine physicians, and nutritionists to develop a holistic treatment plan integrating pharmacologic and non-pharmacologic interventions.
- Schedule regular follow-up appointments to monitor treatment efficacy, assess side effects, and make necessary adjustments to optimize outcomes and ensure patient safety.
- Provide comprehensive education to patients and their families about RLS and PLMD,

treatment options, lifestyle modifications, and the importance of adherence to medication and follow-up appointments.

- Involve patients and their families in shared decision-making, considering their preferences, values, and goals when formulating treatment plans, to enhance engagement and improve treatment adherence.

DISCLOSURE

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