Drugs and Therapeutics Backgrounder:

Iron therapy and restless leg syndrome

Iron deficiency is a secondary cause and exacerbating factor for restless leg syndrome (RLS). If serum ferritin is below 75 ug/L, iron supplementation is recommended to replete iron stores.

Background:

Restless Legs Syndrome (RLS) affects approximately 5%–10% of the population, with a higher prevalence in women over the age of 35. RLS impacts sleep, daytime functioning, cognitive performance, and mood.[1] Brain iron deficiency is implicated in the pathogenesis of RLS, potentially explaining the efficacy of iron administration.[2] Iron replacement therapy improves the severity of RLS, and consensus guidelines suggest evaluation of iron stores in all patients presenting with RLS symptoms. Iron stores should be repleted when appropriate before initiating first-line medications, particularly if serum ferritin is ≤ 75 µg/L .[2-9]

Efficacy

The choice of iron supplementation with oral or intravenous (IV) formulations is dependent on iron indices.[9] Iron therapy has been investigated as a treatment for RLS in both anemic and non-anemic patients.[10] A 2019 systematic review and meta-analysis and a 2019 Cochrane review both demonstrated reduction in RLS symptoms with iron therapy, with no significant subgroup differences between oral and IV iron.[11,12]

Guidance[7] The following does not replace clinicians' judgment

Scenario	Recommended Intervention
Adults	
Serum ferritin ≤ 75 ng/ml **or** transferrin saturation < 20%	**Oral Iron** • ferrous sulfate (conditional recommendation)
Serum ferritin 76-100 ng/ml **Or** need for rapid response due to severity **Or** malabsorption state **Or** intolerance or failure to respond to oral iron	**IV Iron** • Iron sucrose • Ferric derisomaltose (Non-Formulary Do Not Provide status in AHS) • Ferric carboxymaltose (strong recommendation, Non-Formulary Do Not Provide status in AHS)
Pediatrics	
Serum ferritin < 50 ng/mL	• Oral Iron: ferrous sulfate (conditional recommendation)

Safety

Oral iron administration is easier and more convenient than the IV route, but is often limited by gastrointestinal (GI) adverse effects as well as reduced absorption such as in patients with small bowel pathologies, resulting in reduced patient adherence and limited clinical application.[4,13] IV iron offers the advantage of replenishing iron stores with fewer administrations and GI side effects than oral therapy, but is less convenient and carries a low risk of serious infusion reactions.[10]

The 2019 systematic review and meta-analysis by Avni et al. raised concerns about adverse events (AEs) linked to iron therapy, comparing oral and IV iron to placebo. Both iron forms showed higher AEs than placebo, with oral iron contributing to more AEs.[11] Trials with RLS patients have not shown

statistically significant risks with IV iron, though a trend towards headaches was noted. A recent meta-analysis by Qadri et al. demonstrated that IV ferric carboxymaltose significantly improved RLS severity scores and quality of life, and the risk of headaches was found to be non-significant.[14] While some studies suggest that IV iron may increase the risk of infection, more recent studies have not proven this correlation.[15,16] Trials in RLS may be underpowered to detect AEs, raising a need for high quality RCTs to better assess risks of IV iron. Patient engagement in discussions around risks and benefits of iron therapy and consideration of patient comorbidities, can help clinicians provide individualized RLS care.

Alternative Treatments for RLS [6, 17, 18]

Drug	Strength of recommendation in the 2025 RLS Guideline	Reported side effects*
Gabapentin	Strong	Ataxia, dizziness, fatigue, depression, edema, weight gain, infection
Pregabalin	Strong	Peripheral edema, weight gain, xerostomia, dizziness/drowsiness, blurred vision, and visual field loss
IV ferric carboxymaltose	Strong	Hypophosphatemia, flushing, hypertension, N/V**, injection-site reactions, hypersensitivity reactions, and headaches
Opioids	Conditional	Pruritus, dizziness, respiratory depression, N/V, constipation, fever, confusion, depression, neuralgia, and withdrawal syndromes
Peroneal nerve stimulation	Conditional	Not easily available nor covered by all health plans. Transient increase in RLS symptoms, skin irritation, pain, and muscle fatigue

*= list is not reflective of all side effects and only includes common adverse effects reported
**= Nausea and vomiting

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